XIX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

TORINO, CENTRO CONGRESSI LINGOTTO, 5 - 6 MAGGIO 2025

Ruolo dell'anatomopatologo nella diagnosi della GVHD acuta

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Disclosures of Name Surname

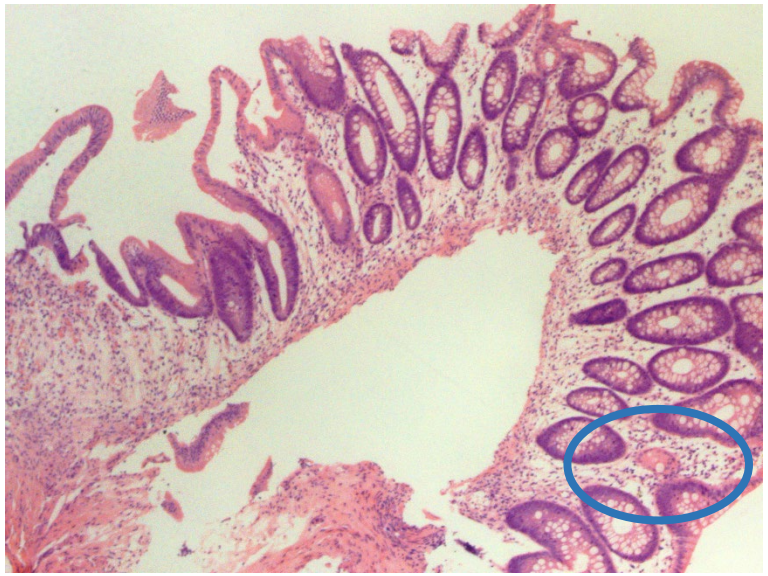
Nothing to declare

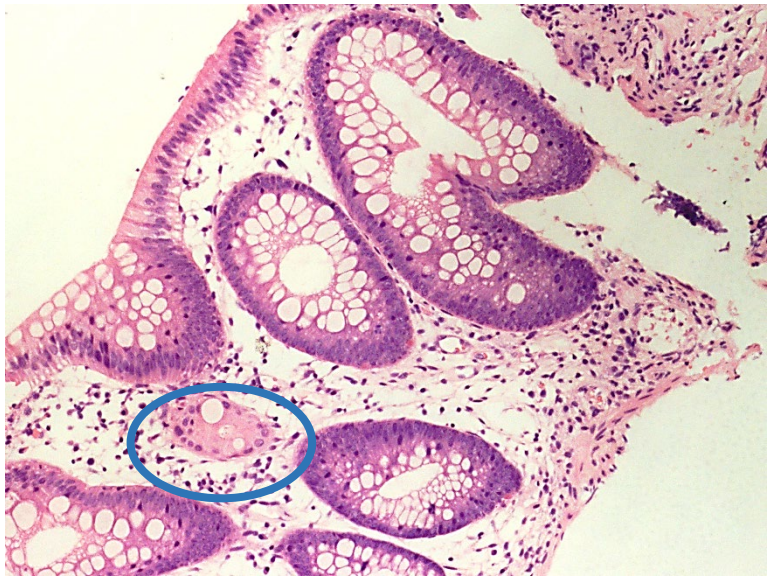
A.S. 01/01/1979, male, HBV+

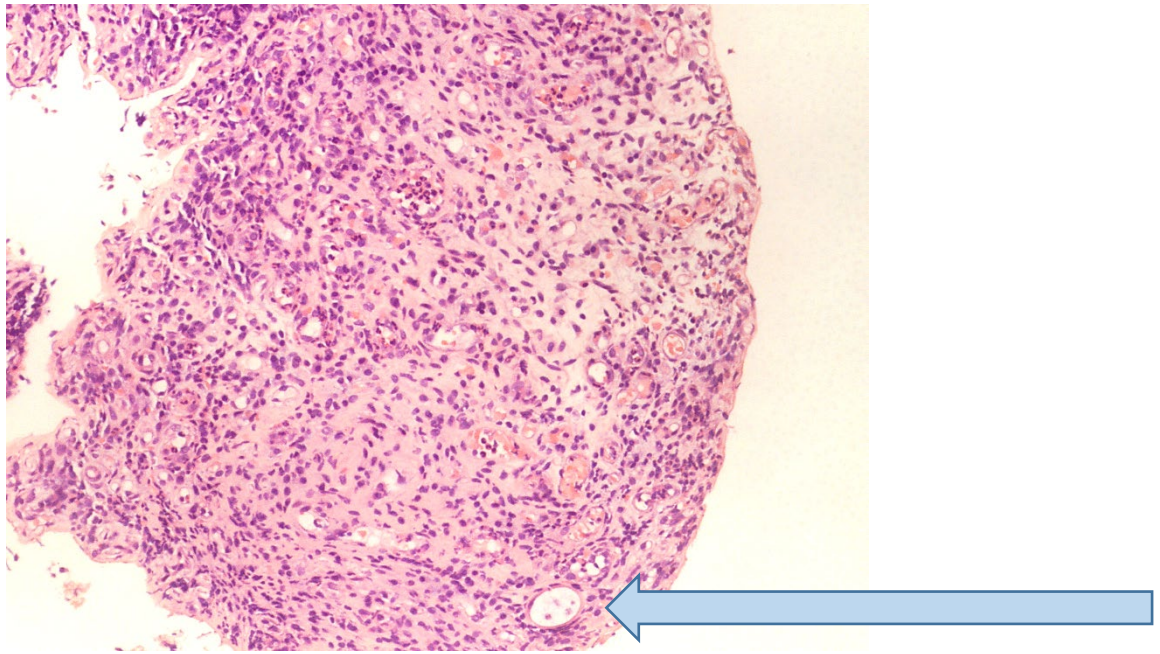
Allogenic BMT for CML 24/06/2022

- Patient with diarrhoea (+37 days) and aGVHD (skin) post transplant for chronic myeloid leukemia.
- Weak positivity for HHV6.
- Colonoscopy: Hypotrophic and fragile ileal mucosa. Edematous and hyperemic colonic mucosa, fragile to the contact with the instrument, with some millimetric aphthae of the left colon.

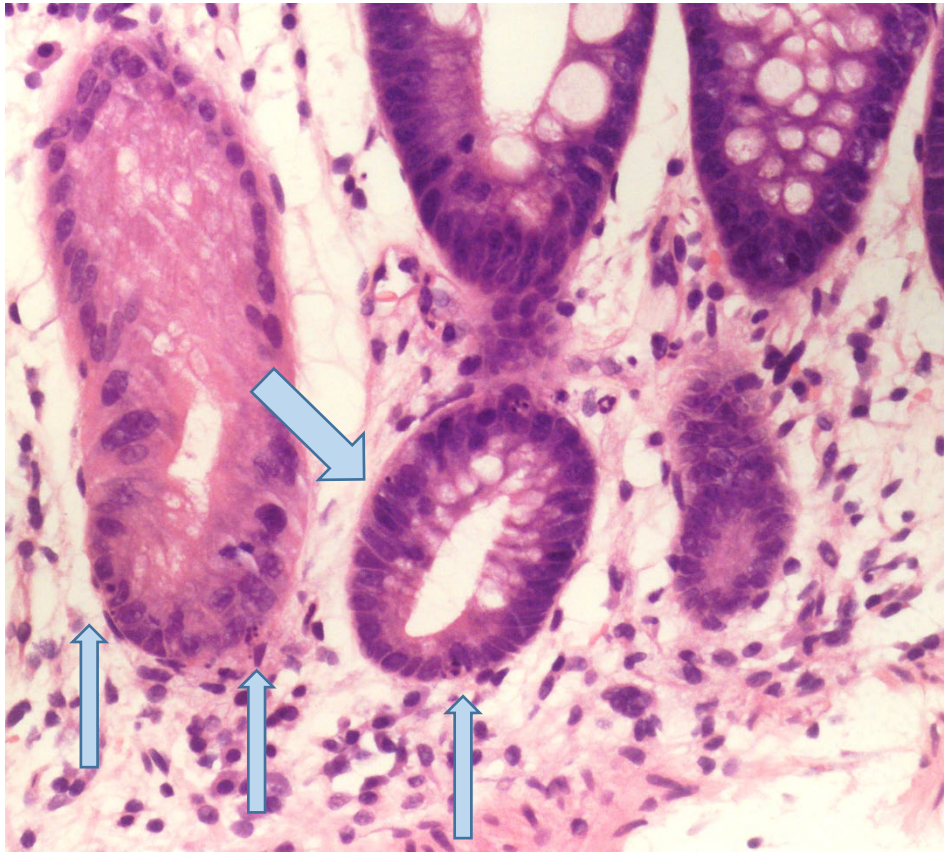
Thanks to Dr.ssa Maria Teresa Lupo Stanghellini (Ospedale San Raffaele Milano)





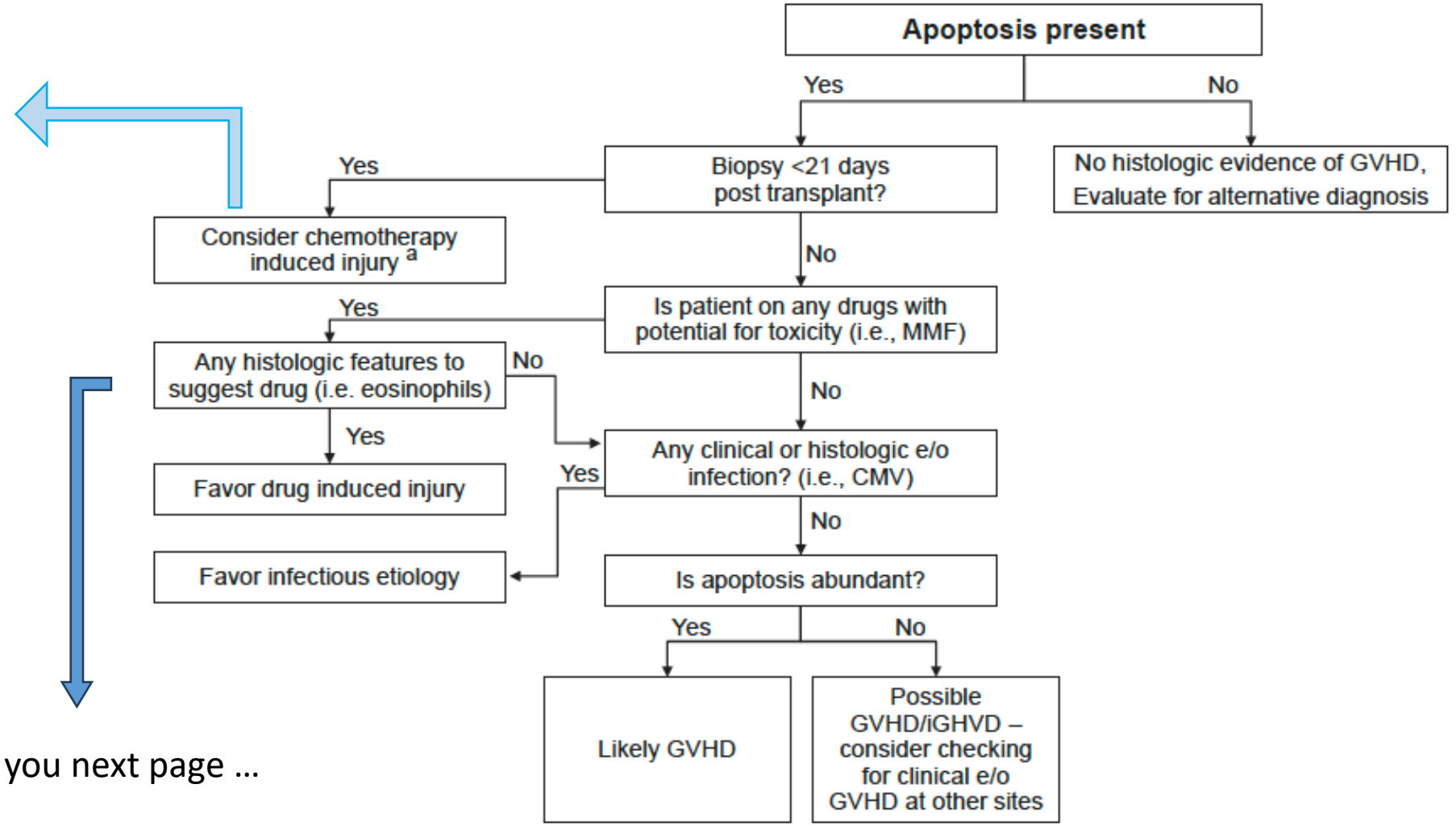


Apoptotic features!! But heterogeneous distribution



Cytotoxic effect of conditioning chemotherapy and total body irradiation (first 3 weeks!!, resolving by 21 days post BMT)

Autologous transplant or close to 21-day



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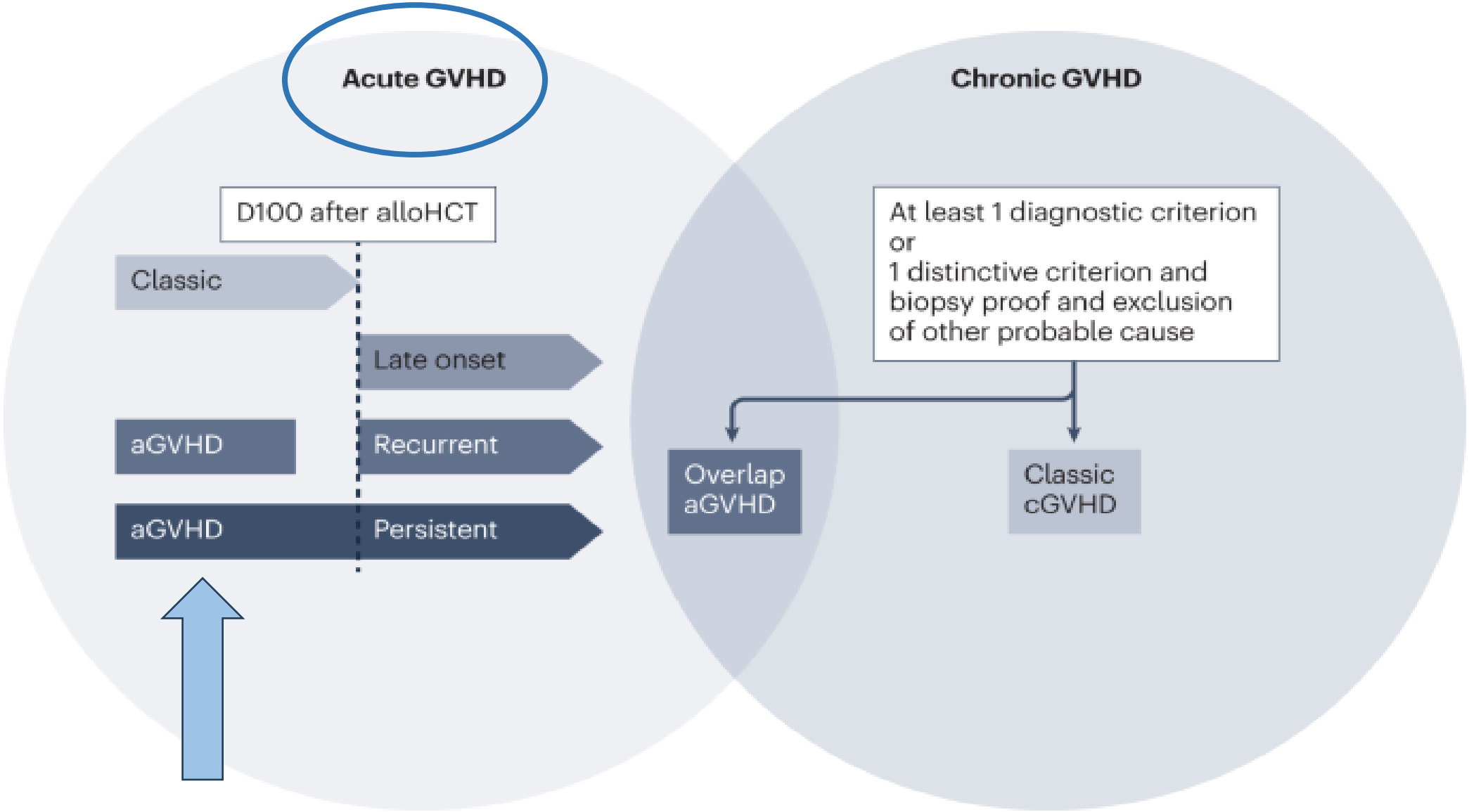
Zhang T et al, Surgical Pathology Clinics 16 (2023) 745–753

Acute vs chronic graft versus host disease



*Malard F et al, Acute graft-versus-host disease. Nat Rev Dis Primers **9**, 27 (2023)*

ELSEVIER

Biology of Blood and Marrow Transplantation

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Report

NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: II. The 2014 Pathology Working Group Report

Table 1
Histological Criteria for GVHD by Organ System

Organ or System	Minimal Criteria for Acute/Active GVHD*	Specific Criteria for Chronic GVHD†
Liver	Global assessment of dysmorphic or destroyed small bile ducts ± cholestasis, lobular and portal inflammation	Ductopenia, portal fibrosis, chronic cholestasis reflect chronicity but are not specific for chronic GVHD
GI	Variable apoptotic criteria (≥1/piece) in crypts	Destruction of glands, ulceration or submucosal fibrosis may reflect severe or long-standing disease but are not specific for chronic GVHD

- Differentiating acute from chronic GVHD on biopsy material is not always possible.
- Features of acute GVHD may present even in organs that have defined criteria for chronic GVHD.
- The exact threshold at which a diagnosis of GVHD may be made with confidence remains not established.

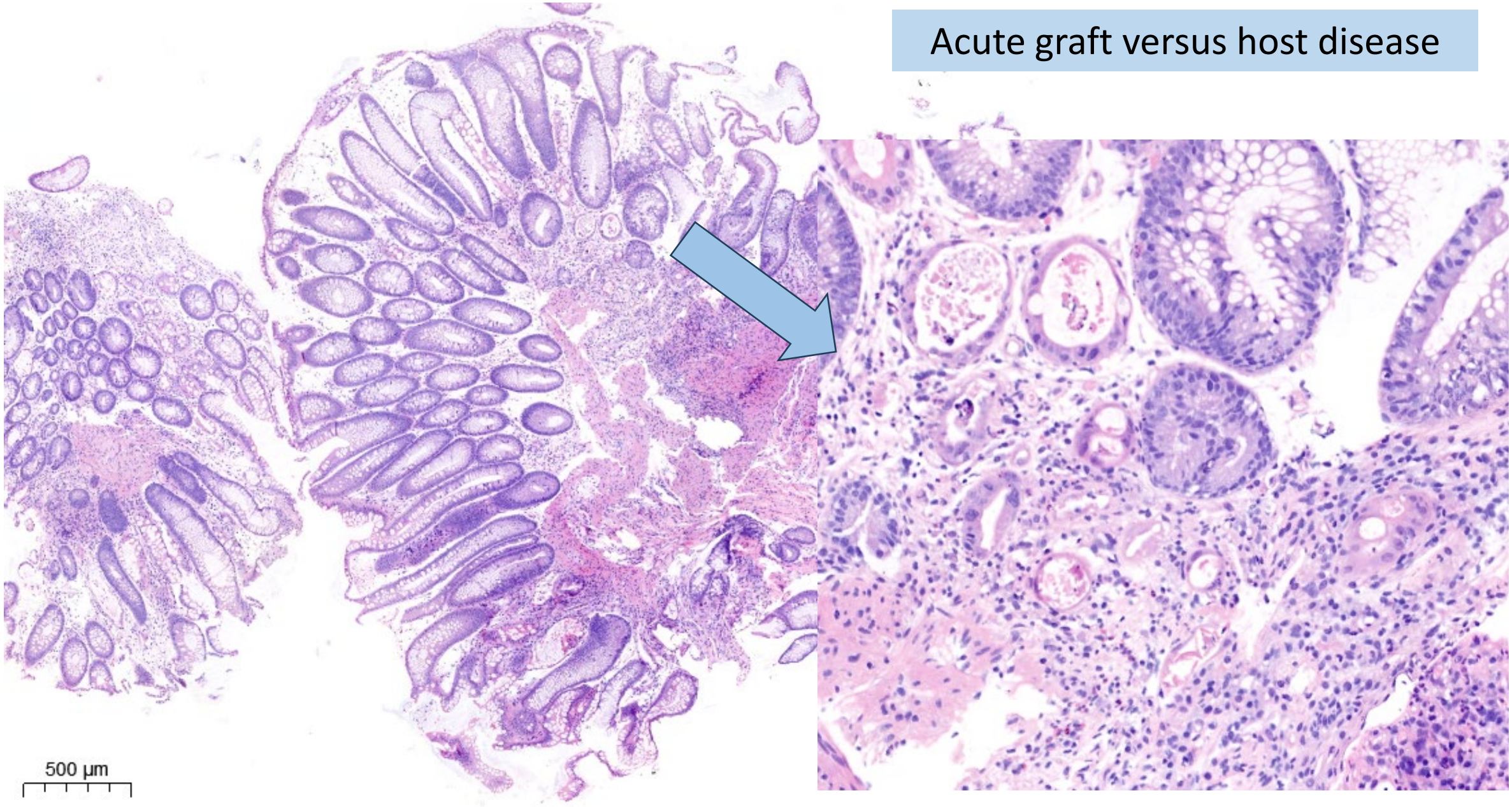
Shulman et al, Biol Blood Marrow Transplant 21 (2015) 589-603

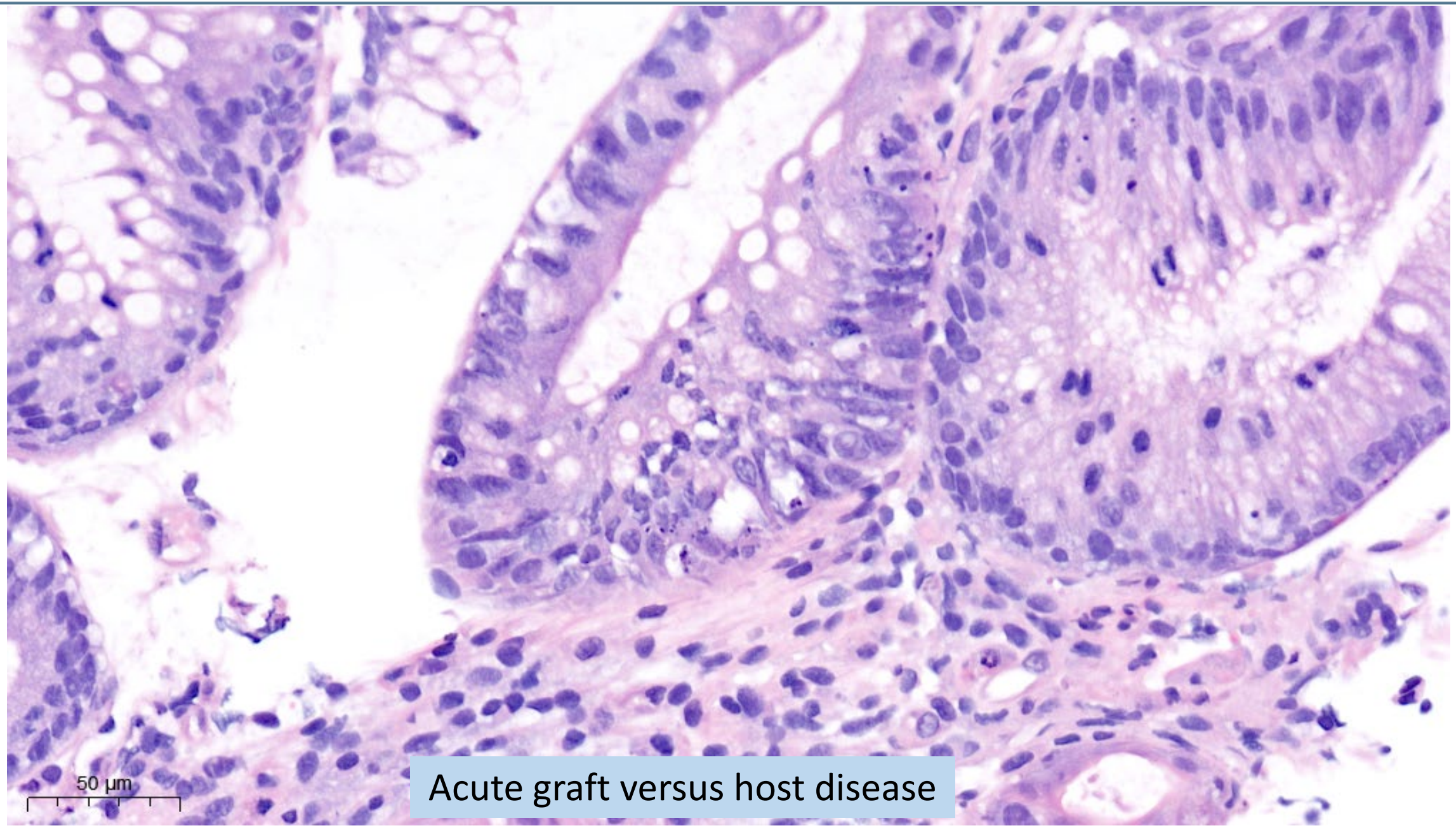
Table 3
Distinguishing histologic features of the differential diagnosis

	Crypt Apoptosis	Eosinophilic or Neutrophilic Inflammation	Apoptotic Microabscesses	Lerner Grade 4 Disease with Neuroendocrine Aggregates	Viral Cytopathic Effect
GVHD	++	+/–	++	+	-
Drug-induced injury	+	++	+/–	-	-
Infection (CMV)	+	+/–	-	-	+

Zhang T et al, Surgical Pathology Clinics 16 (2023) 745–753

Acute graft versus host disease





Acute graft versus host disease

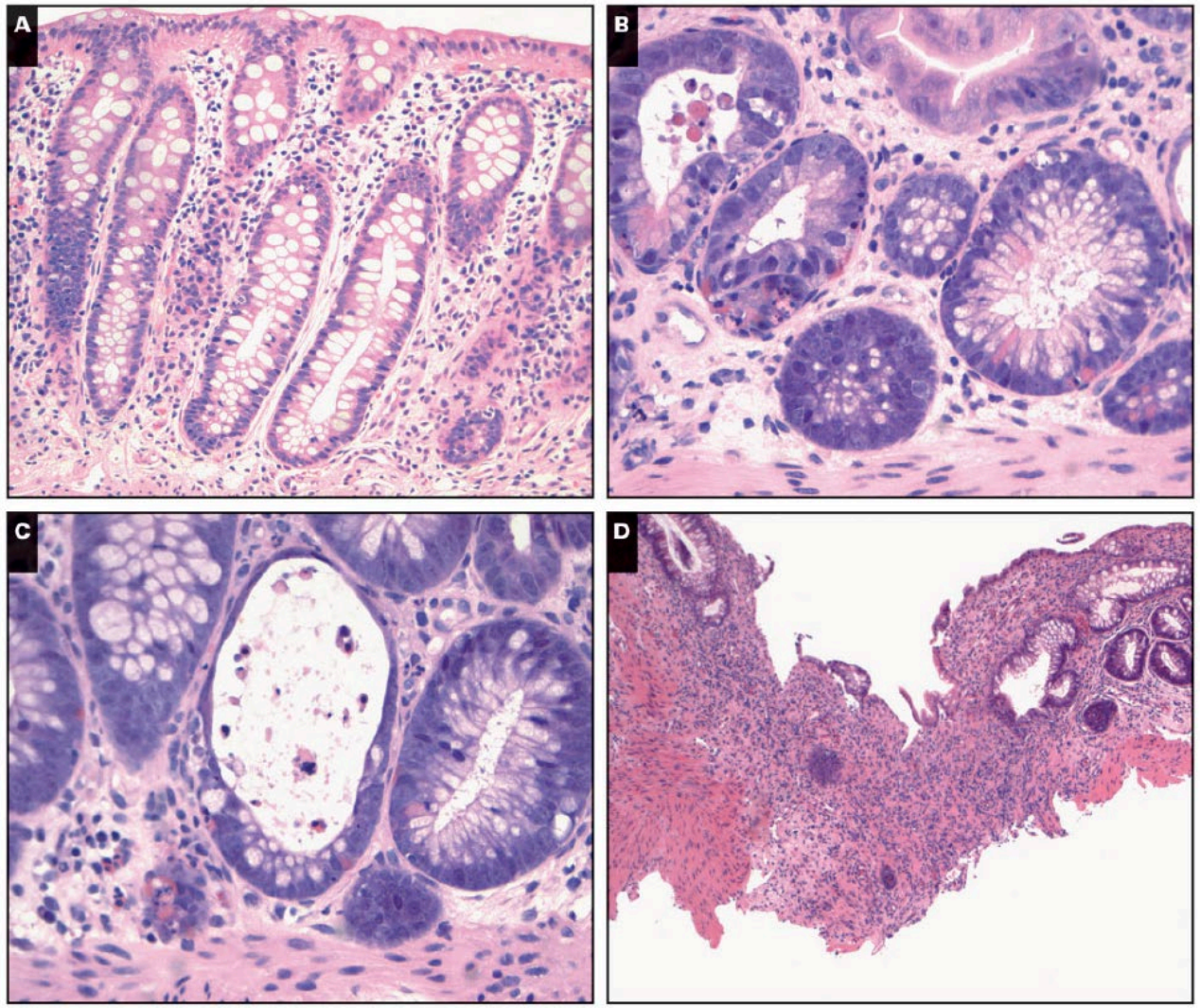


Table 1
Modified grading system for acute graft-versus-host disease described by Lerner

Grade 1	Isolated apoptotic epithelial cells, without crypt loss
Grade 2	Loss of isolated crypts, without loss of contiguous crypts
Grade 3	Loss of two or more contiguous crypts
Grade 4	Extensive crypt loss with mucosal denudation

- GVHD of the gut develops in over 50% of all allogeneic HSCT recipients and is nearly always a component of clinically severe cases.
- GVHD may have a ***patchy distribution*** even within in a single region
- The tissue blocks should be serially sectioned as well.

Salomao M et al, Am J Clin Pathol 2016;145:591-603

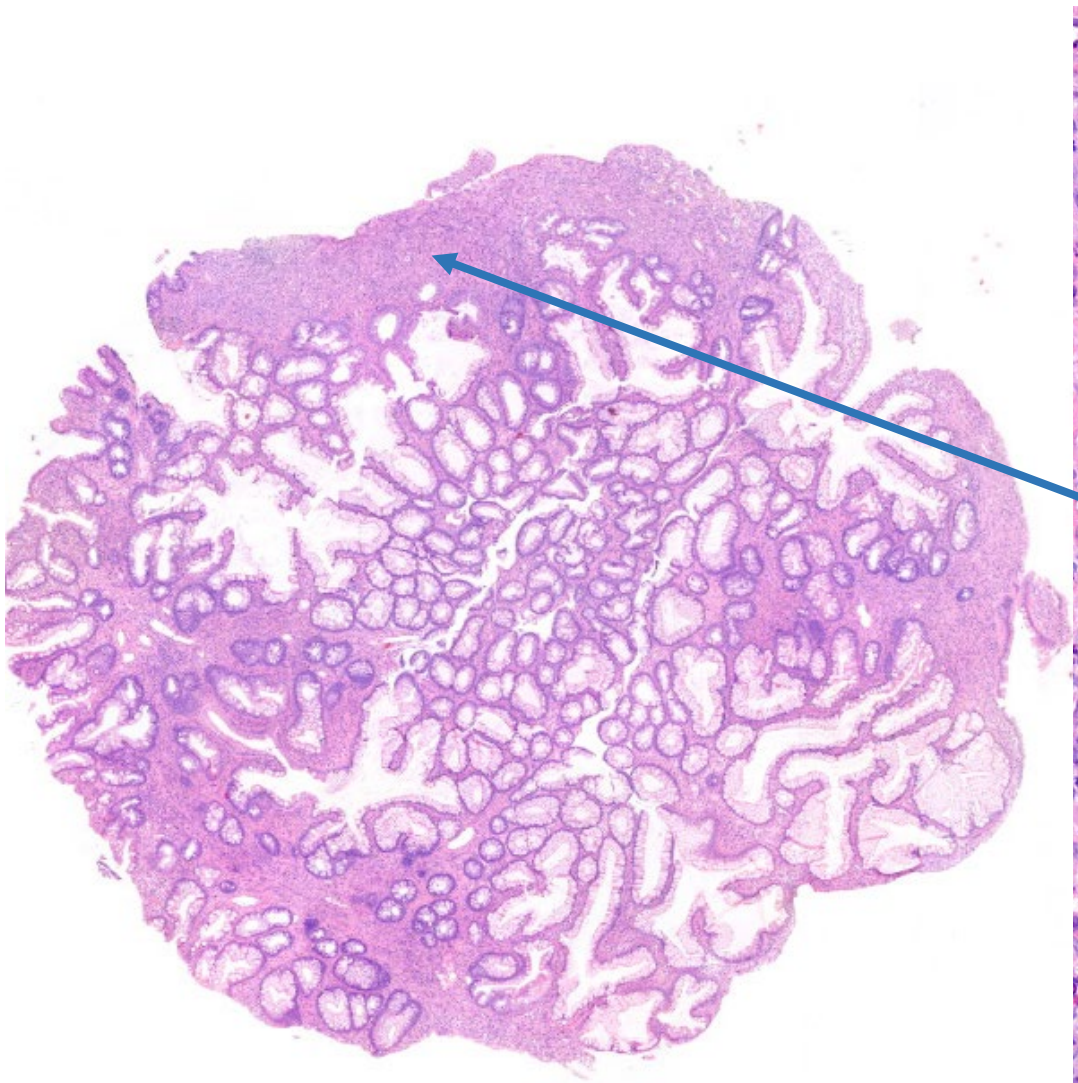
Zhang T et al, Surgical Pathology Clinics 16 (2023) 745–753

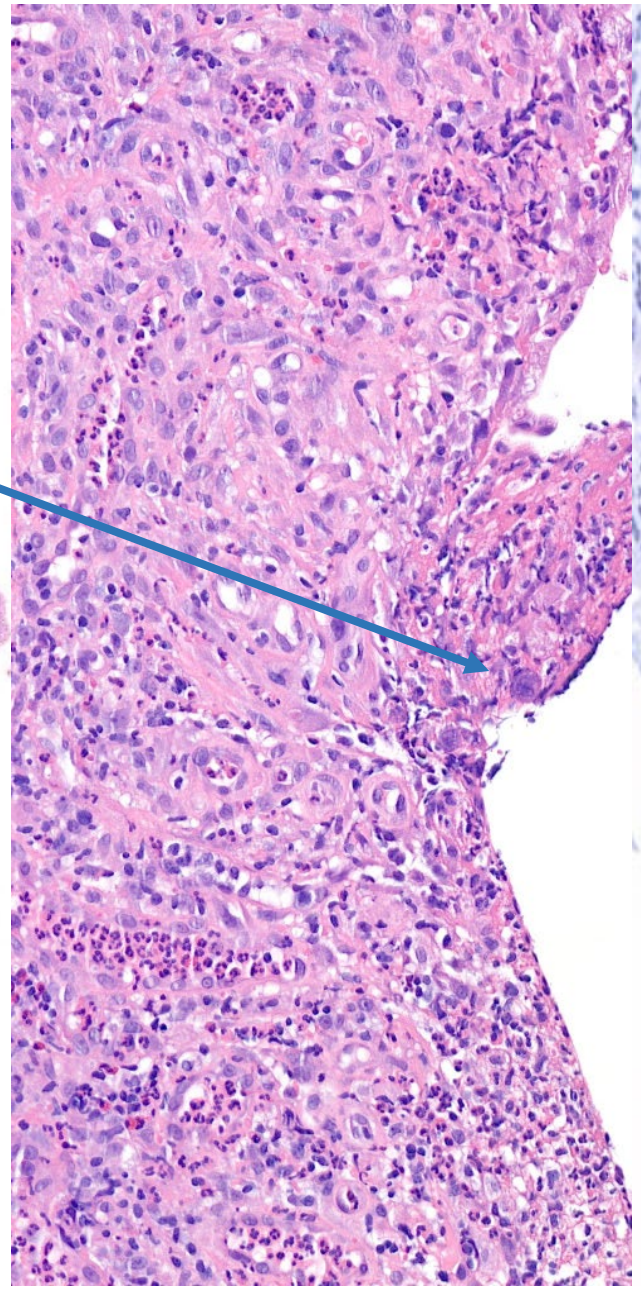
Table 3

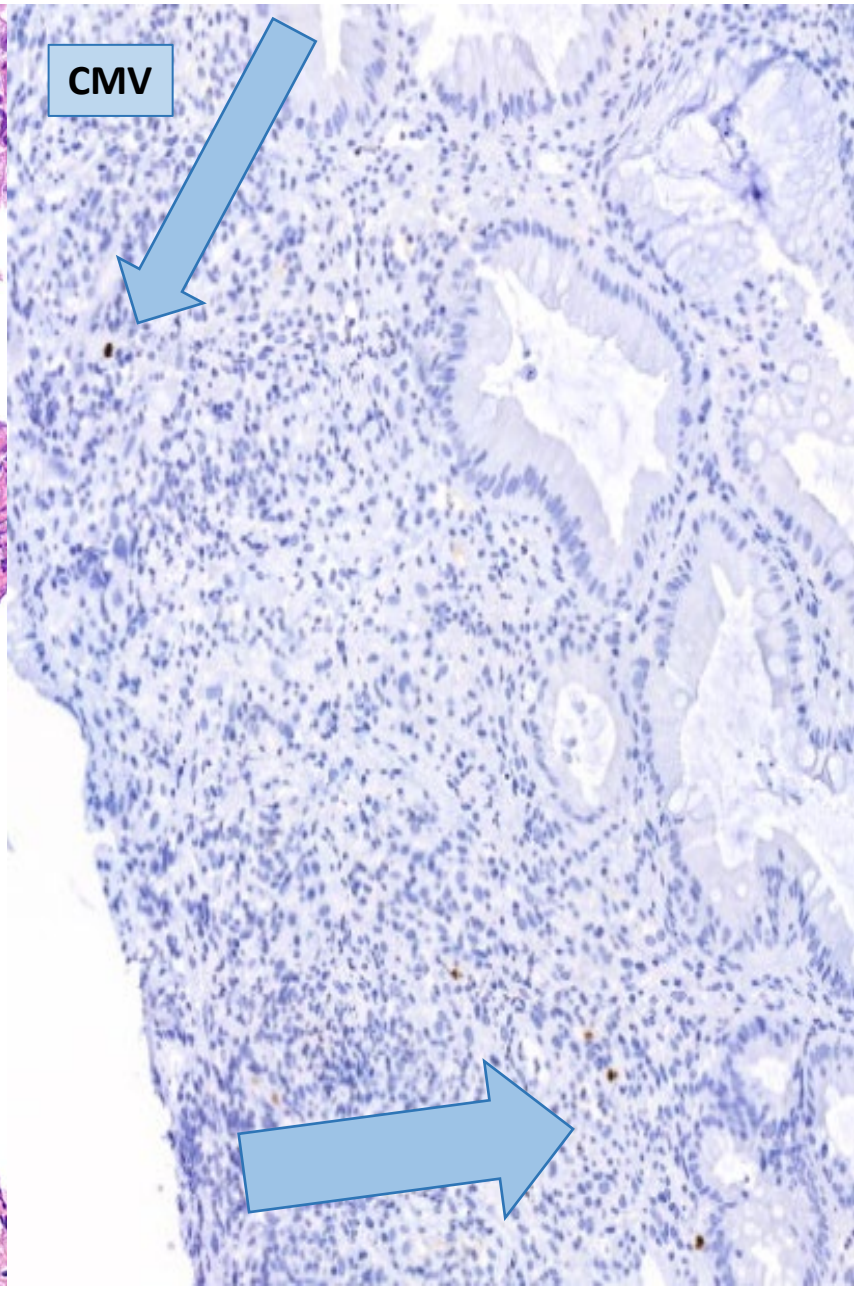
Differential Diagnosis of Gastrointestinal Graft-vs-Host Disease

Conditioning regimen	
Infections	
CMV, *Adenovirus*	Viral inclusions, ulceration, routine IHC recommended
Clostridium difficile, *Cryptosporidium parvum*, *Campylobacter*, *Helicobacter pylori*	Presence of pseudomembranes, organisms at surface epithelium, correlate with stools cultures/PCR
Medications	
Mycophenolate mofetil	Eosinophils, neuroendocrine cell aggregates, lack of crypt abscesses
NSAIDs	
Ticlopidine	
Proton pump inhibitors	Only affects stomach, mild
5-FU, cyclosporine	
Bowel preparation	

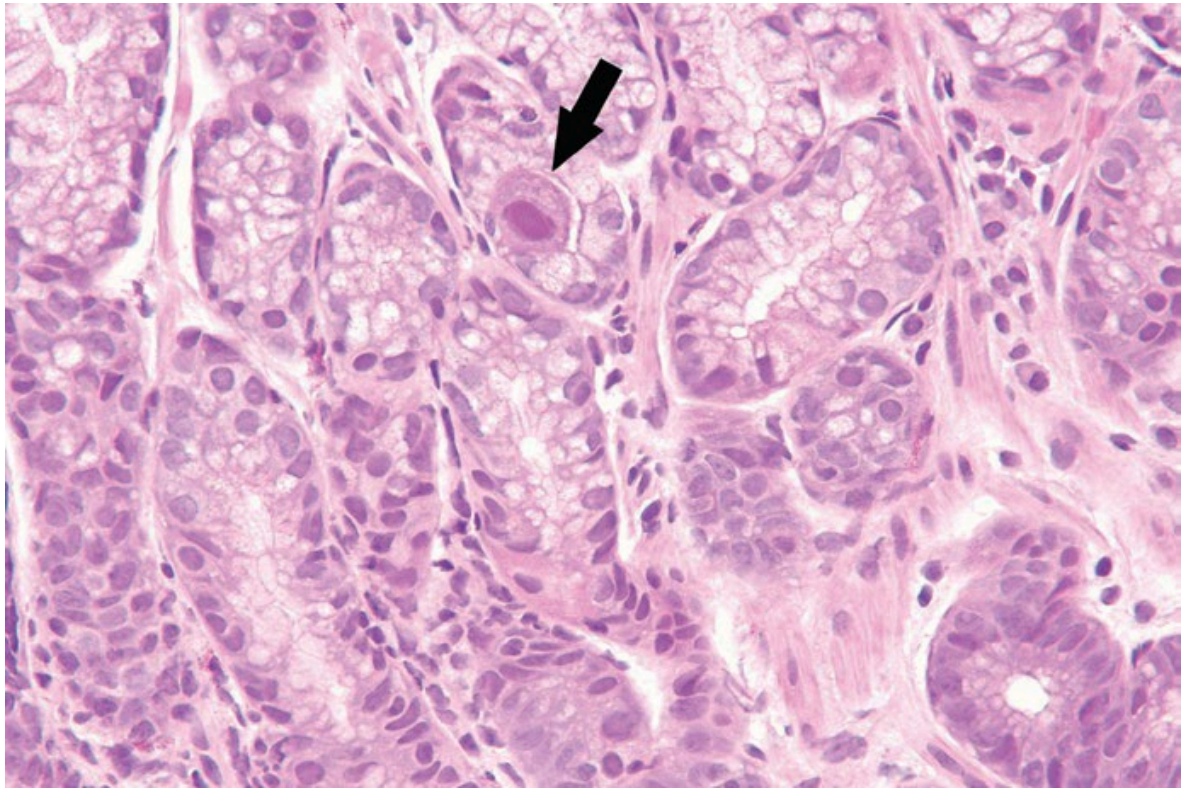
No alterations of the crypts!!

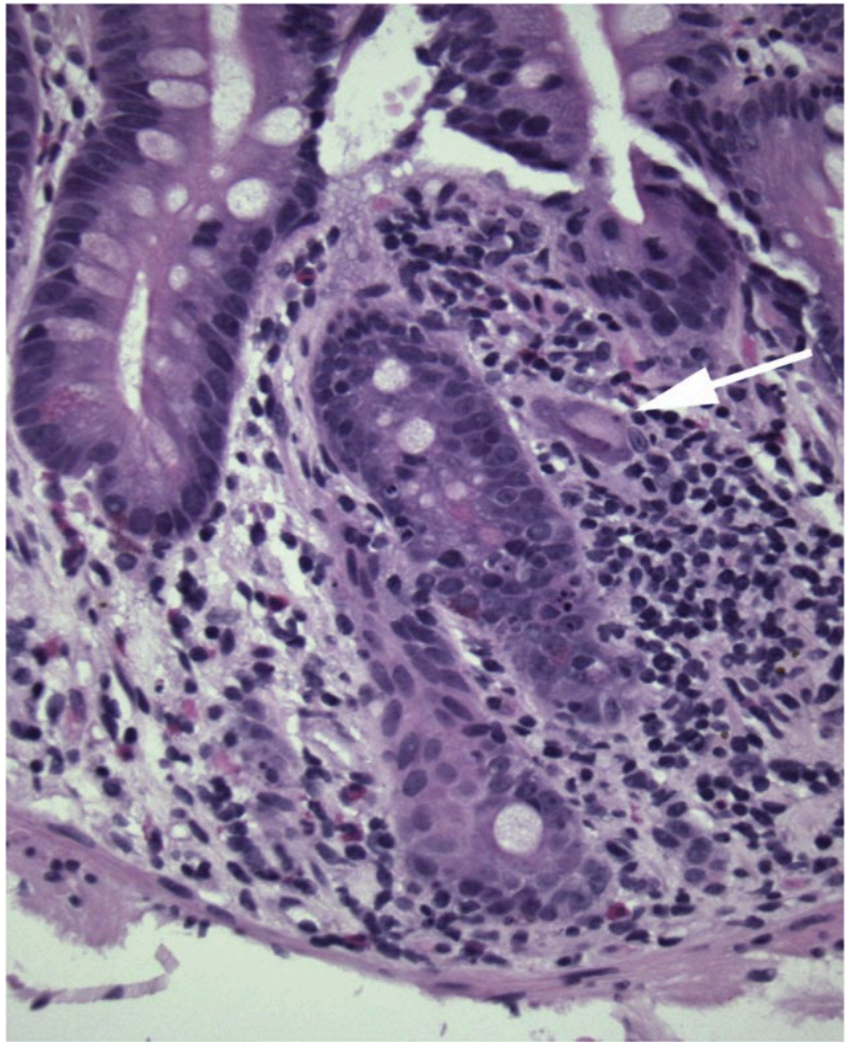





CMV

Citomegalovirus (CMV)



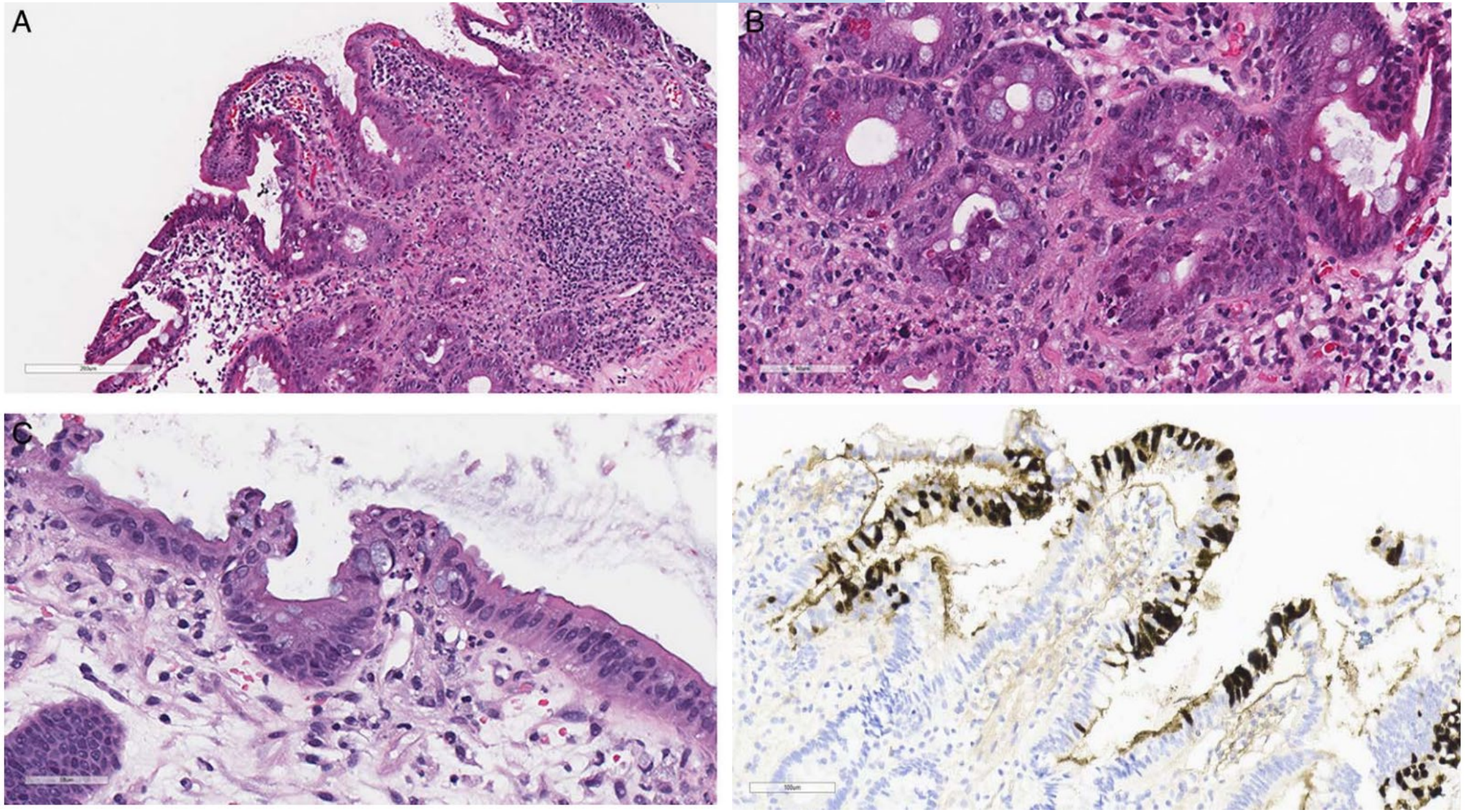


- occurrence of acute graft-versus-host disease (GVHD) significantly increased the risk of CMV infection and of subsequent CMV pneumonia (The Journal of Infectious Diseases, Volume 153, Issue 3, March 1986, Pages 478- 488)
- **PERFORM IMMUNOHISTOCHEMISTRY!!**

A diagnosis of "possible GVHD" is recommended if apoptotic bodies are located in the same crypt or gland as CMV inclusions and a diagnosis of "consistent with GVHD" if abundant apoptosis not associated with CMV inclusions is present.

Washington K et al, Human Pathology (2009) 40, 909–917

Adenovirus



Hissong E et al, Am J Surg Pathol 2024;48:521–527

Adenovirus

- incidence of infection among HSCT recipients ranges from **3% to 47%.**
- Children and patients with either allogeneic transplants or concomitant acute graft-versus-host disease (GVHD) are at ***higher risk*** for developing infection
- respiratory tract, gastrointestinal tract, and urinary bladder
- Disseminated disease occurs in up to 20% of patients who are associated with multiorgan failure and high mortality rates
- The ***duodenum*** was the most frequently affected site of infection (62%), followed by the colon (56%) and terminal ileum (47%); multifocal gastrointestinal tract involvement was present in 20 (62%)
- Intranuclear viral inclusions were identified in the superficial epithelium in 28 (88%) of study cases, though they were often rare and difficult to detect

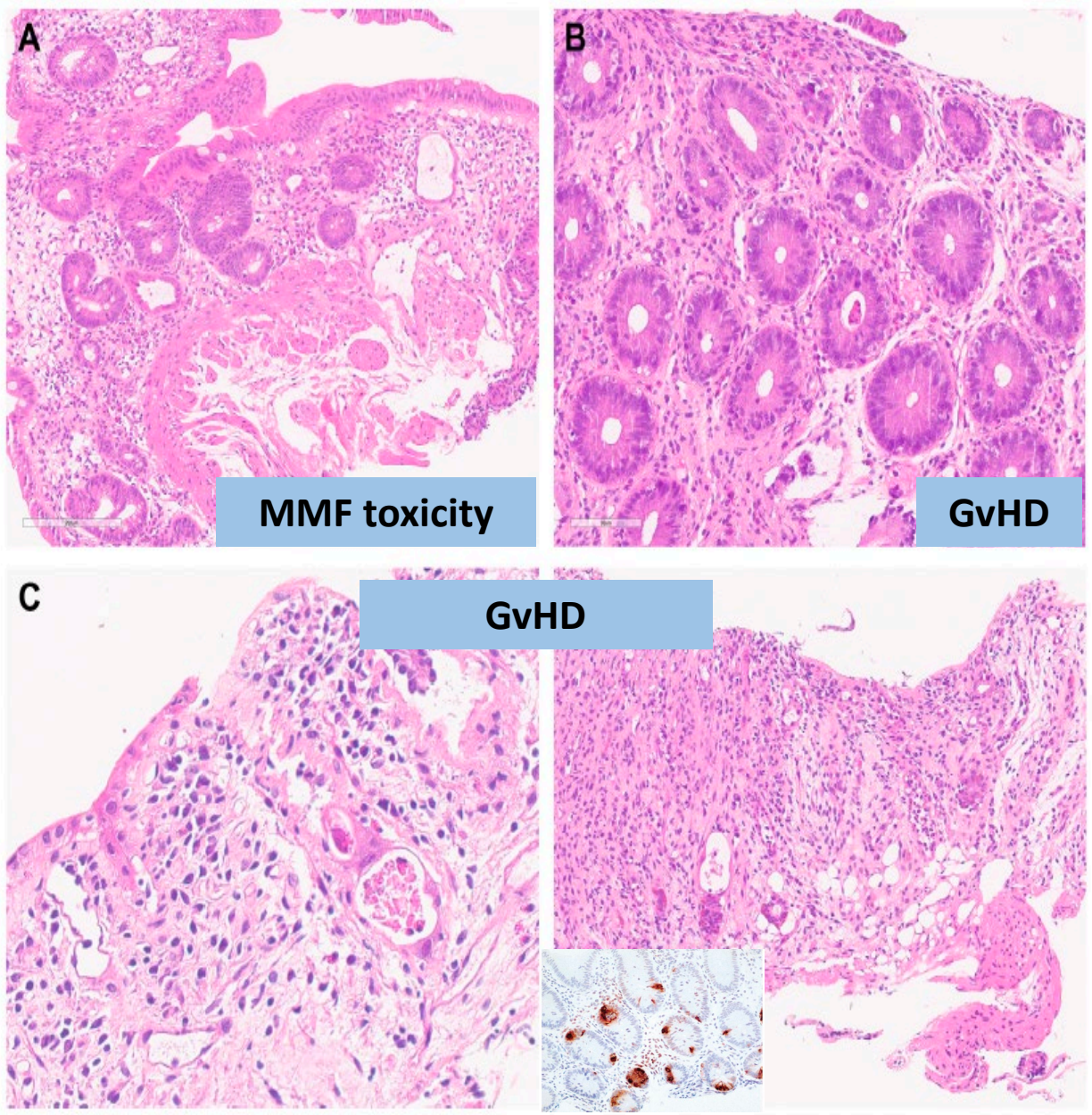
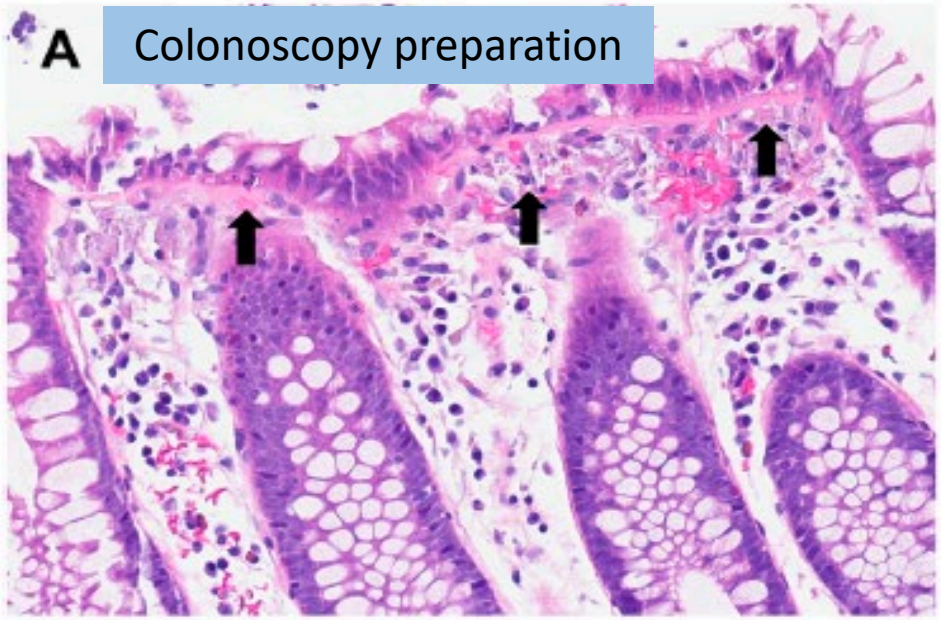
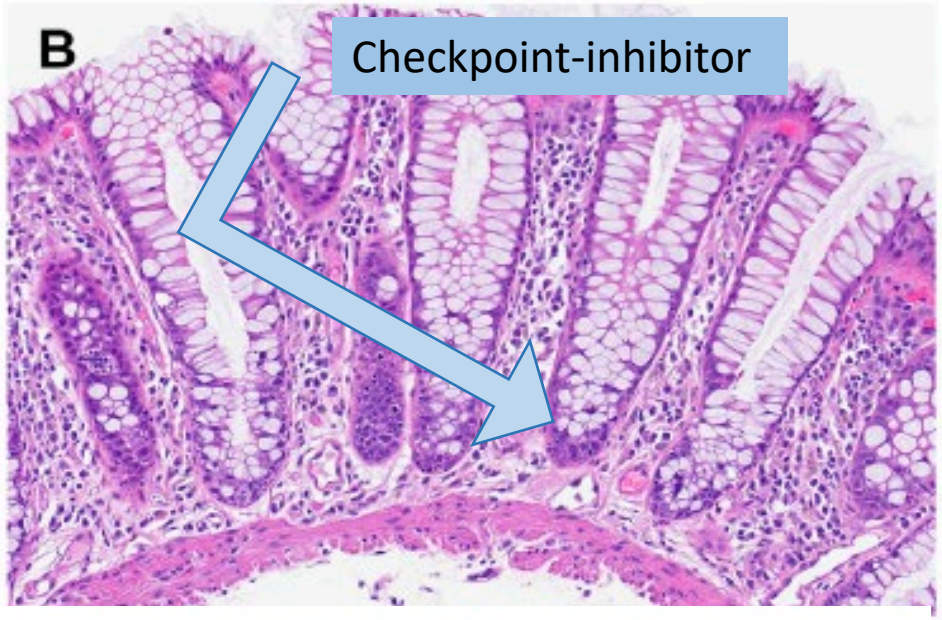


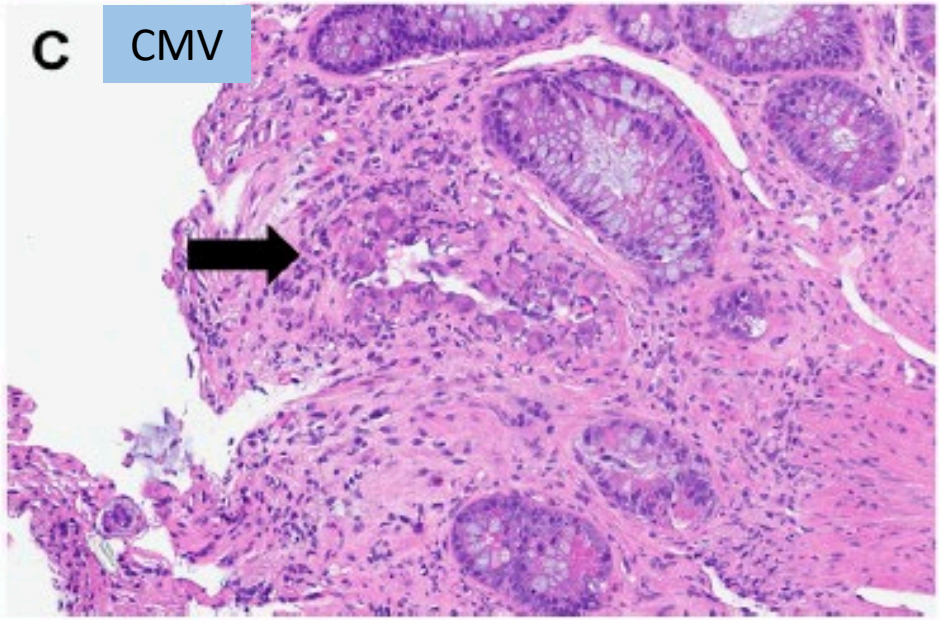
Table 3. Comparison of Histologic Features in Mycophenolate Acid (MFA)–Induced Colitis and Graft-versus-Host Disease (GVHD)

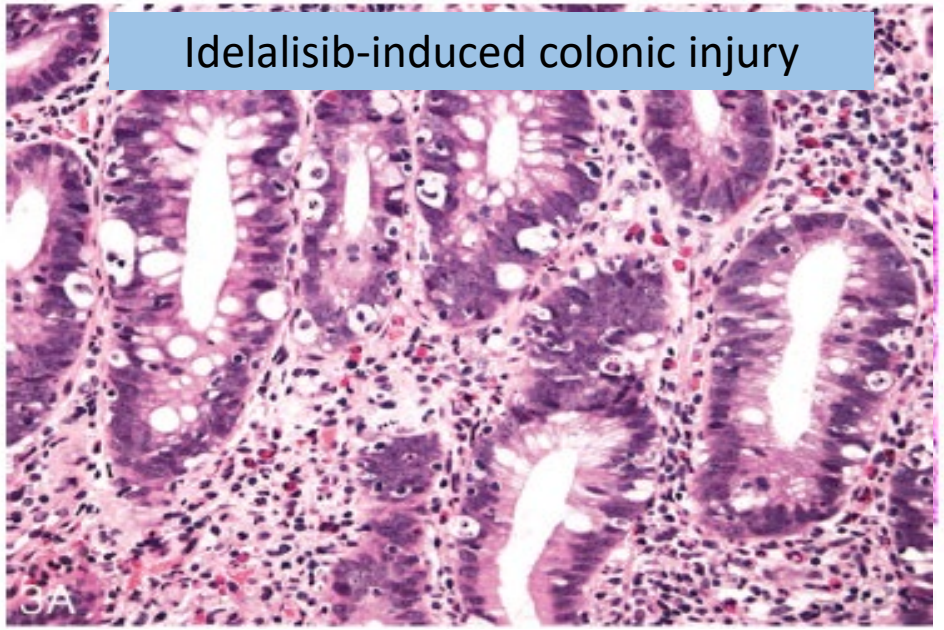
Histologic Features	MFA-Induced Colitis	GVHD
Lamina propria eosinophils	Numerous (>15 per 10 HPF)	Rare
Lamina propria endocrine cell aggregates	Absent	Frequent[a]
Crypt distortion	Absent or mild	Frequent[a]
Neutrophilic abscesses	Rare or absent	Frequent[a]
Eosinophilic abscesses	Rare	Frequent[a]
Acute cryptitis	Rare	Frequent[a]
Apoptoses	Frequent	Frequent
Apoptotic microabscesses	Absent	Frequent
Hypereosinophilic (degenerated) crypts	Present	Frequent[a]

Zhang T et al, Surgical Pathology Clinics 16 (2023) 745–753









Zhang T et al, Surgical Pathology Clinics 16 (2023) 745–753; Esmeralda Celia Marginean, Arch Pathol Lab Med. 2016;140:748–758

Idelalisib-associated Colitis

Histologic Findings in 14 Patients

Anna-Sophie Weidner, MD, Nicole C. Panarelli, MD,* Julia T. Geyer, MD,* Erica B. Bhavsar, BS,† Richard R. Furman, MD,† John P. Leonard, MD,† Jose Jessurun, MD,* and Rhonda K. Yantiss, MD**

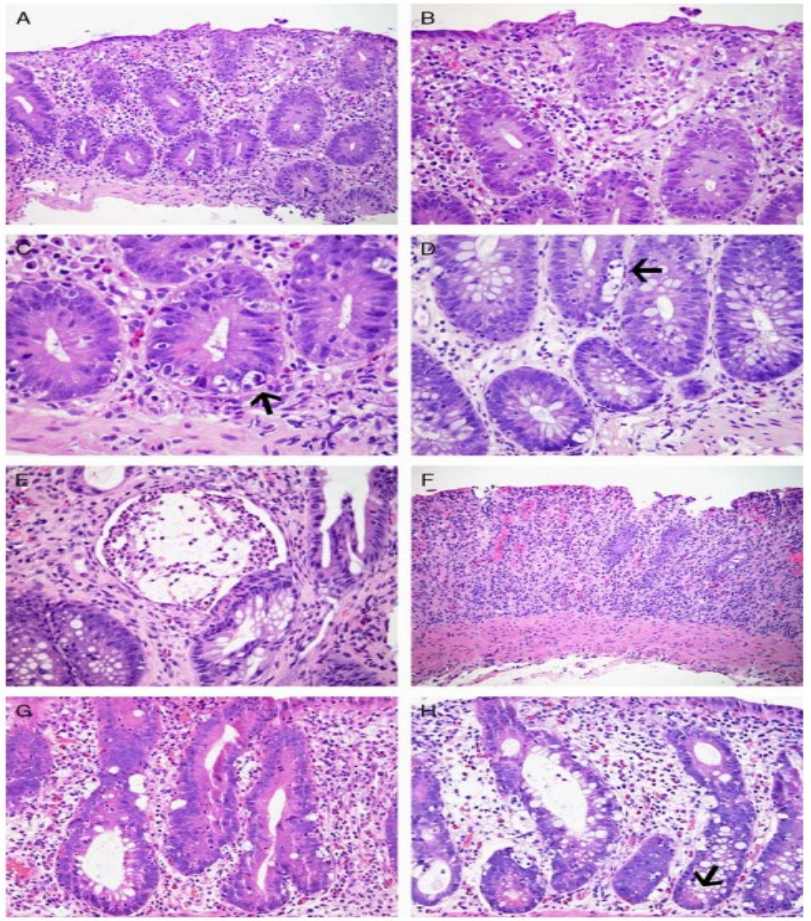
TABLE 1. Clinical Features of Patients With Gastrointestinal Symptoms After Idelalisib Treatment

Patient	Age (y)	Sex	Underlying Disease	Severity of Diarrhea	Endoscopic Appearance	Histologic Abnormalities	Outcome
1	77	Female	CLL	Grade ≥ 3	Severe pancolitis	Yes	Improvement with idelalisib cessation and intravenous/oral corticosteroids
2	63	Male	CLL	Grade ≥ 3	Severe pancolitis	Yes	Improvement with idelalisib cessation and oral corticosteroids
3	60	Male	MZL	Grade ≥ 3	Mild pancolitis	Yes	Improvement with idelalisib cessation and oral corticosteroids
4	66	Male	CLL	Grade ≥ 3	Moderate colitis	Yes	Improvement with idelalisib cessation and oral corticosteroids
5	60	Male	CLL	Grade ≥ 3	Moderate colitis	Yes	Improvement with idelalisib cessation and oral corticosteroids
6	72	Male	CLL	Grade ≥ 3	Normal	Yes	Improvement with idelalisib cessation and oral corticosteroids
7	50	Male	FL	Grade ≥ 3	Moderate pancolitis	Yes	Improvement with oral corticosteroids; idelalisib continued
8	47	Male	CLL	Grade ≥ 3	Normal	Yes	Improvement with bendamustine cessation; idelalisib continued
9	61	Male	CLL	Grade 1-2	Moderate pancolitis	Yes	Improvement with idelalisib cessation and oral corticosteroids
10	67	Female	CLL	Grade 1-2	Normal	Yes	Improvement with idelalisib cessation and oral corticosteroids
11	49	Male	CLL	Grade 1-2	Mild pancolitis	Yes	Improvement with idelalisib cessation and oral corticosteroids
12	63	Female	FL	Grade 1-2	Normal	No	Improvement with idelalisib cessation
13	84	Male	CLL	Grade 1-2	Mild colitis	No	Spontaneous resolution of symptoms
14	68	Male	CLL	Grade 1-2	Mild focal colitis	Yes	Intermittently recurrent symptoms; idelalisib continued
15	76	Female	FL	Grade 1-2	Not performed	NA	Improvement with idelalisib cessation
16	67	Male	CLL	Grade 1-2	Not performed	NA	Symptom resolution with brief interruption of idelalisib therapy
17	64	Male	CLL	Grade 1-2	Not performed	NA	Spontaneous resolution of symptoms
18	54	Male	CLL	Grade 1-2	Not performed	NA	Spontaneous resolution of symptoms
19	79	Male	MCL	Grade 1-2	Not performed	NA	Spontaneous resolution of symptoms
20	67	Female	CLL	Grade 1-2	Not performed	NA	Spontaneous resolution of symptoms
21	74	Male	CLL	Grade 1-2	Not performed	NA	Spontaneous resolution of symptoms
22	62	Female	CLL	Grade 1-2	Not performed	NA	Spontaneous resolution of symptoms
23	50	Male	FL	Grade 1-2	Not performed	NA	Spontaneous resolution of symptoms

Diarrhea grading: grade 1-2 = increase of up to 6 stools per day over baseline; grade ≥ 3 = increase of ≥ 7 stools per day over baseline and/or hospitalization indicated.
CLL indicates chronic lymphocytic leukemia; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NA, not applicable.

TABLE 2. Histologic Features of Colonic Biopsy Specimens From Patients With Idelalisib-associated Diarrhea

Histologic Feature	No. Cases, n (%)
Intraepithelial lymphocytosis	12 (86)
Crypt epithelial cell apoptosis	11 (79)
"Exploding" apoptotic bodies	7 (50)
Neutrophilic cryptitis	11 (79)
Crypt abscesses	8 (57)
Erosion and/or ulcer	4 (29)
Crypt loss	3 (21)
Crypt architectural abnormalities	2 (14)
Paneth cell metaplasia	2 (14)
Viral cytopathic changes	0 (0)



Anna-Sophie Weidner et al. Am J Surg Pathol 2015;39:1661–1667

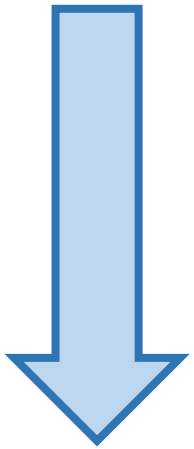
- **Best = sampling upper and lower GI**
- No consensus on limited biopsy strategy
- **MMF-related gut injury can occur both in upper and lower GI tract**
- Loss of intestinal Paneth cells as late occurence in severe GvHD = poor prognosis

- GVHD is a **pauci-inflammatory process** histologically characterized by crypt apoptosis.
- **Apoptosis in the GI tract is nonspecific** (drug-induced injury and infection).
- Significant inflammation (eosinophilic or neutrophilic) can be a histologic clue to underlying medication-related injury.
- GI biopsies from stem cell transplantation patients should be assessed for infectious organisms, particularly CMV.

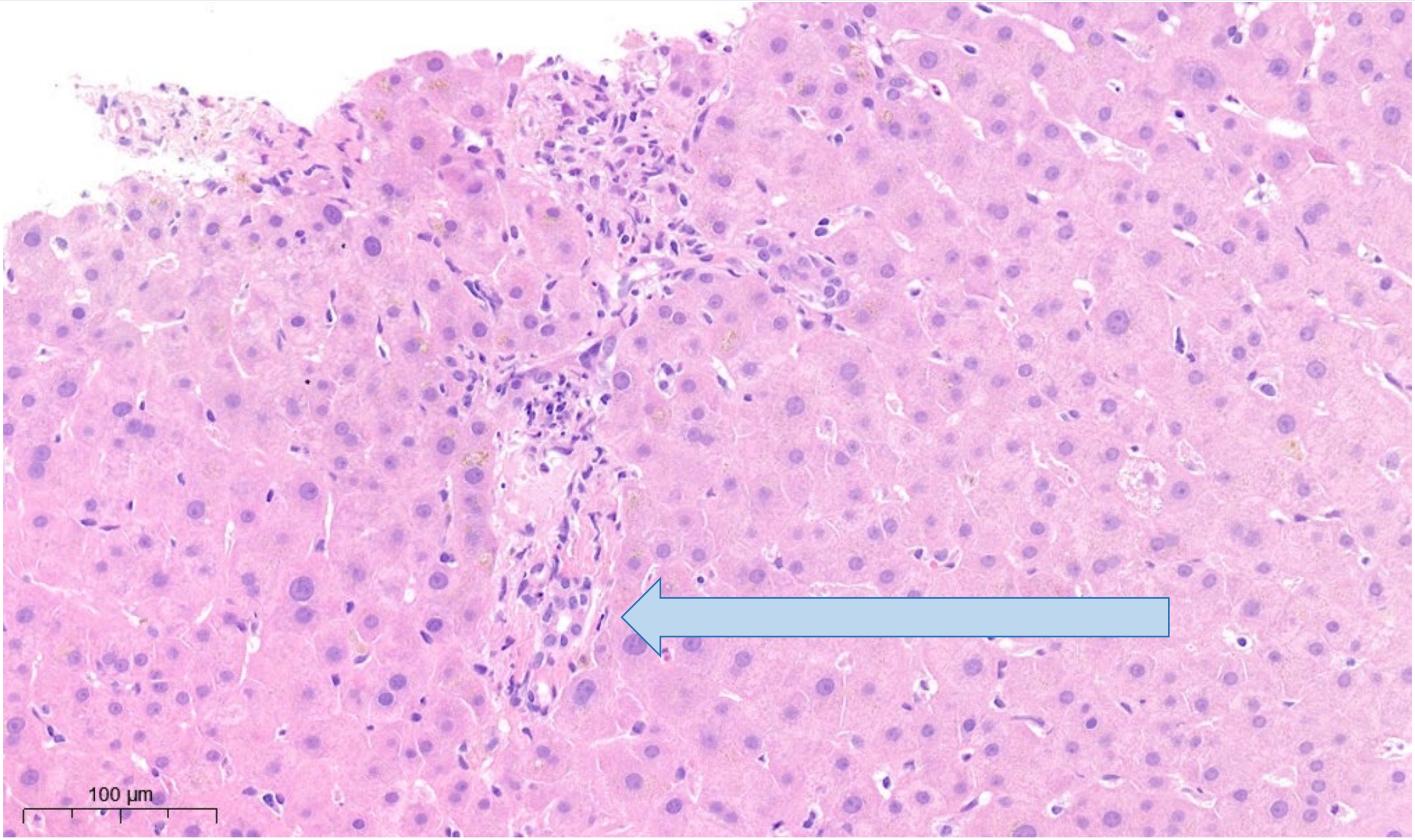
Washington K, Human Pathology (2009) 40, 909–917

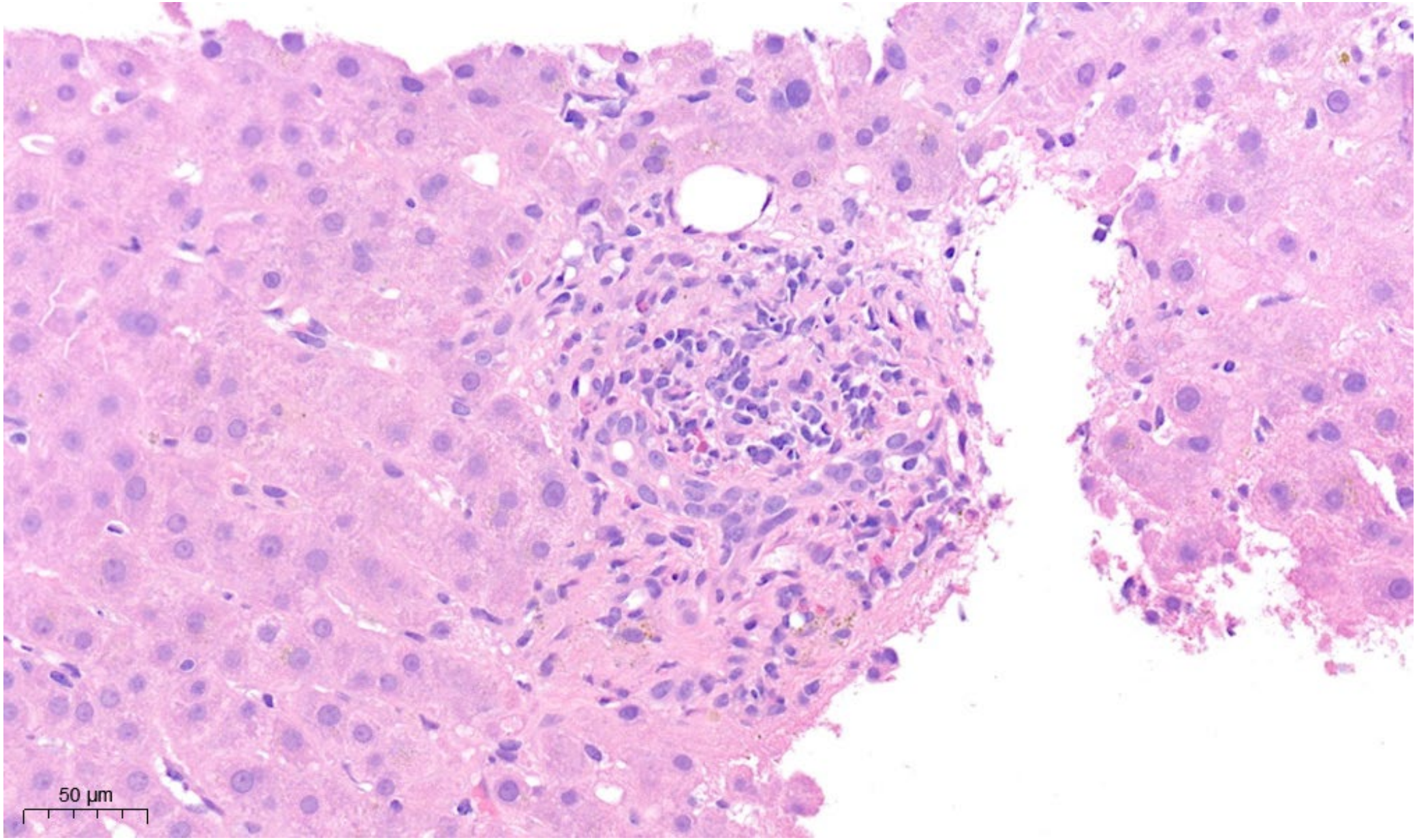
Zhang T et al, Surgical Pathology Clinics 16 (2023) 745–753

- 03/10/2022 increase in stasis indices on therapy with UDCA 300 x 3 (ALP up to 1008, GGT stable around 300, bilirubin always in range). Autoimmunity and viruses negative.
- Non-cirrhotic portal hypertension (portosystemic gradient 8 mmHg, RANGE 3-5 mmHg).

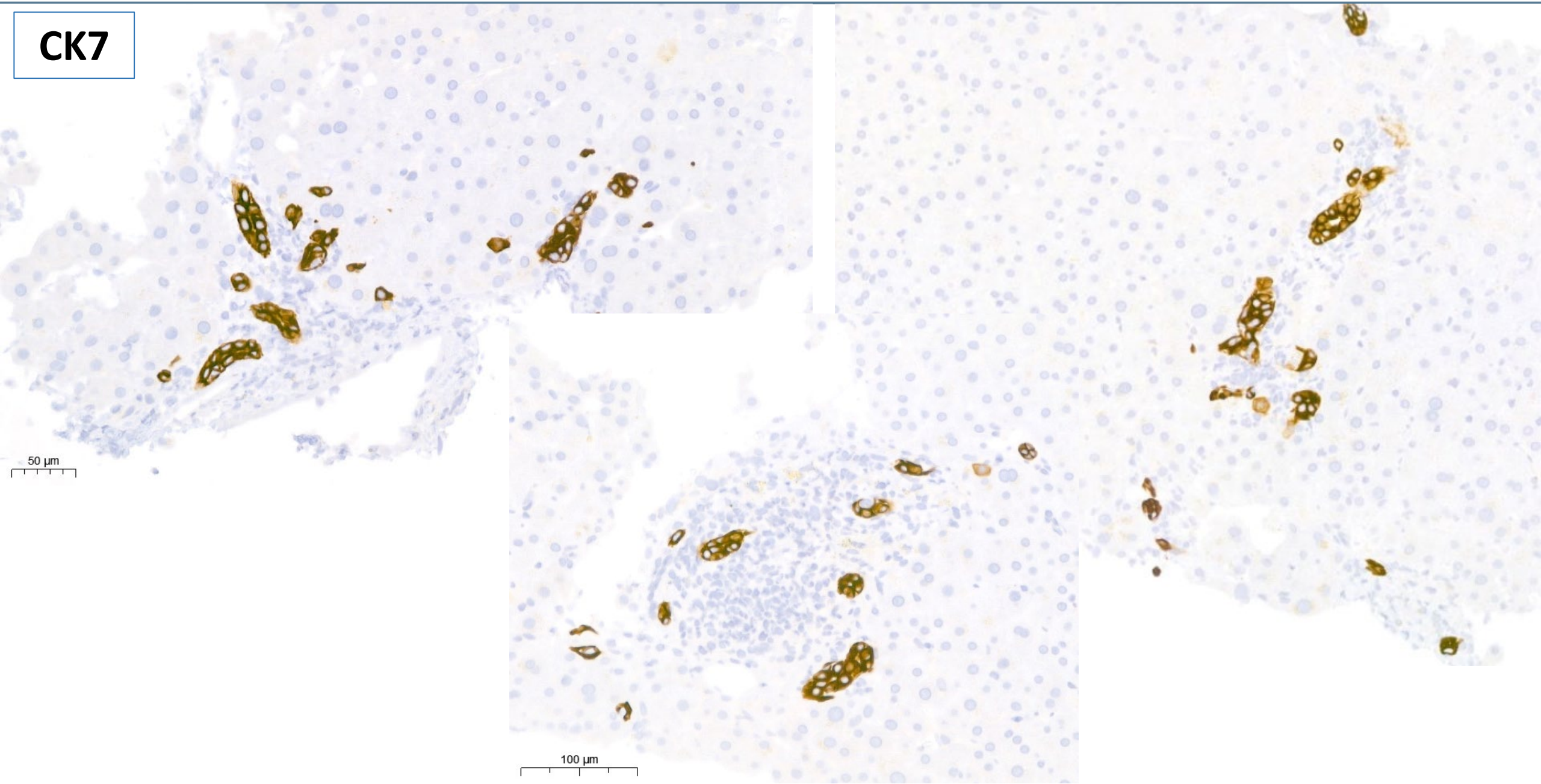


Liver biopsy

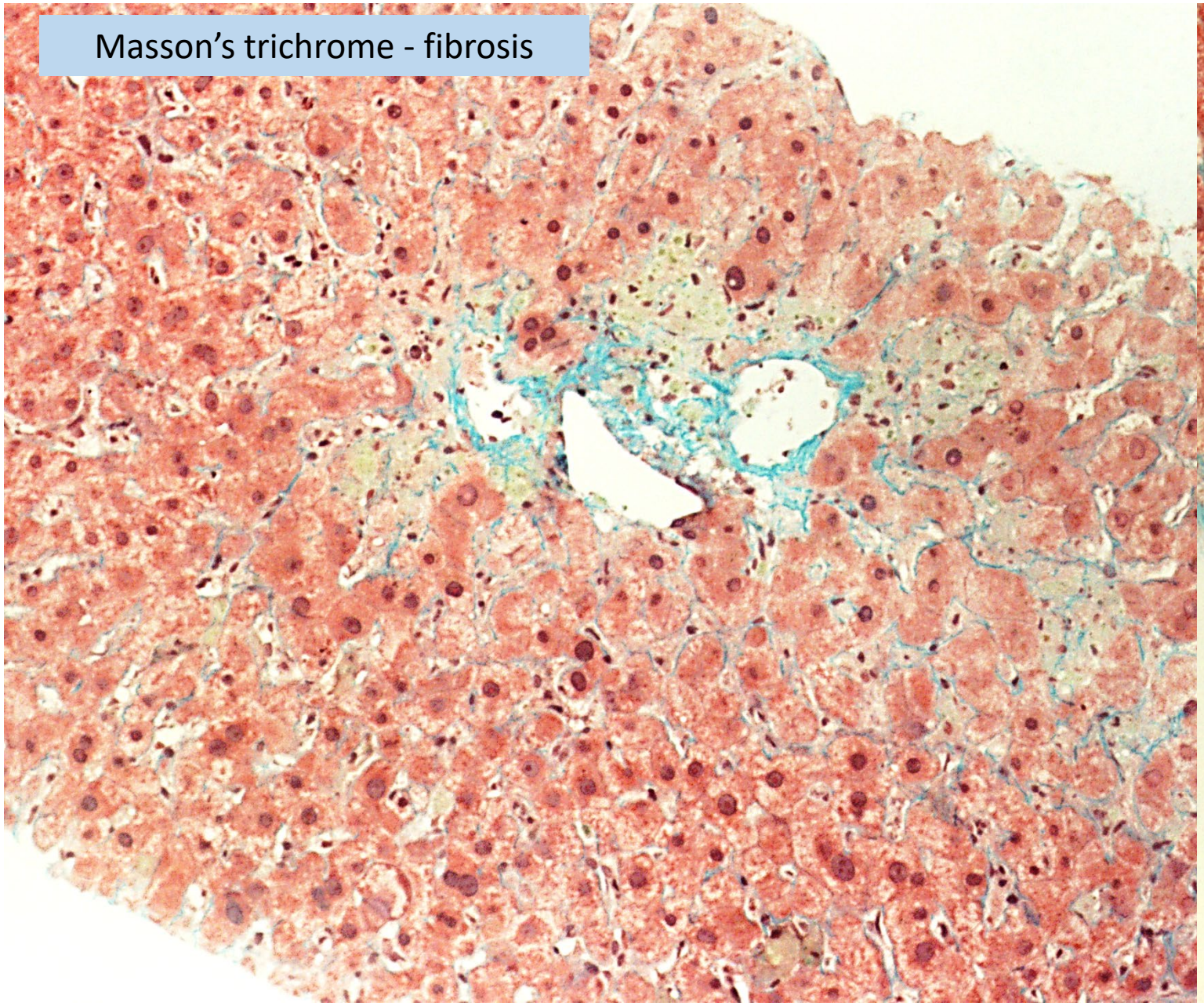

100 µm

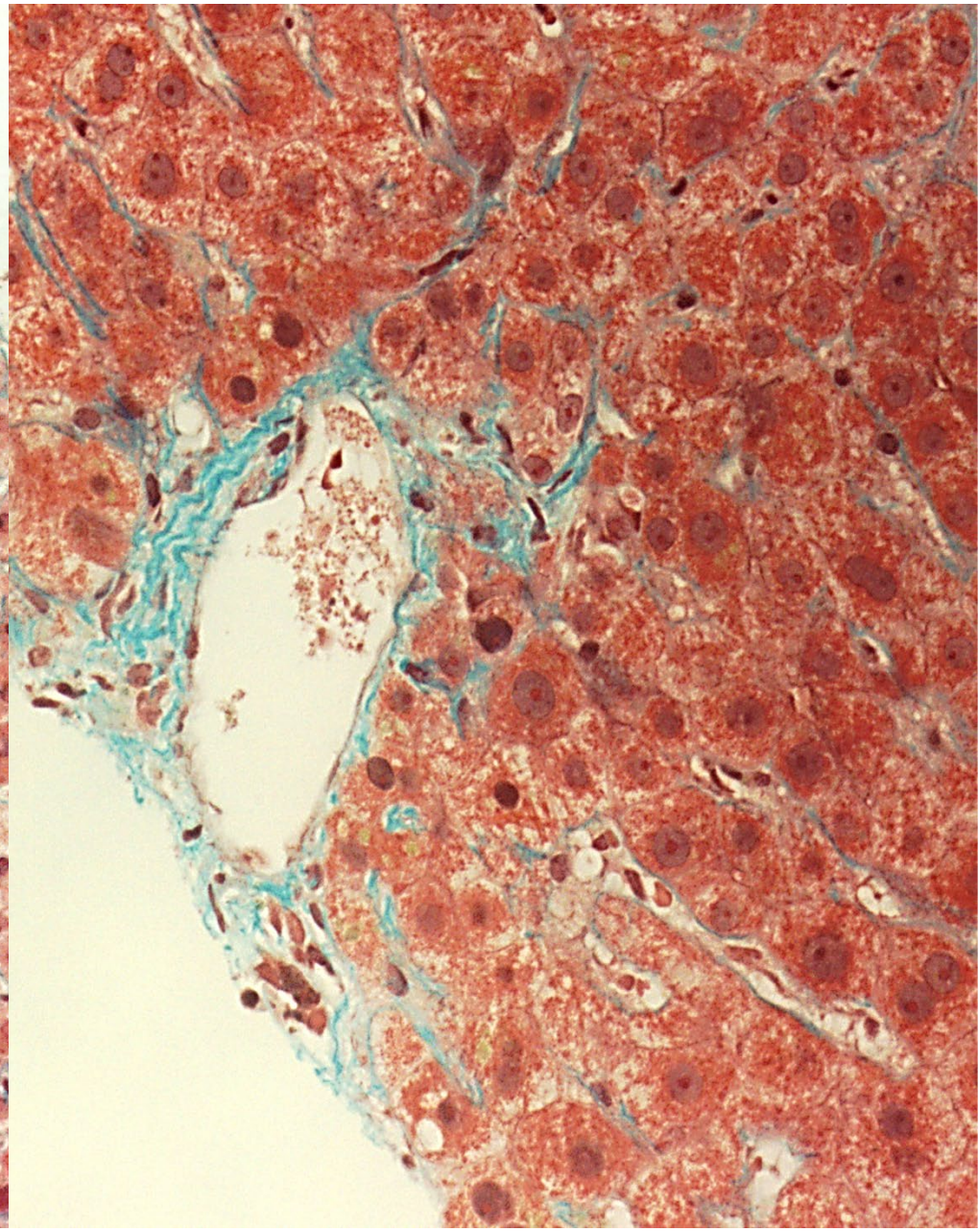

50 µm

CK7



Masson’s trichrome - fibrosis





Vascular damage after BMT

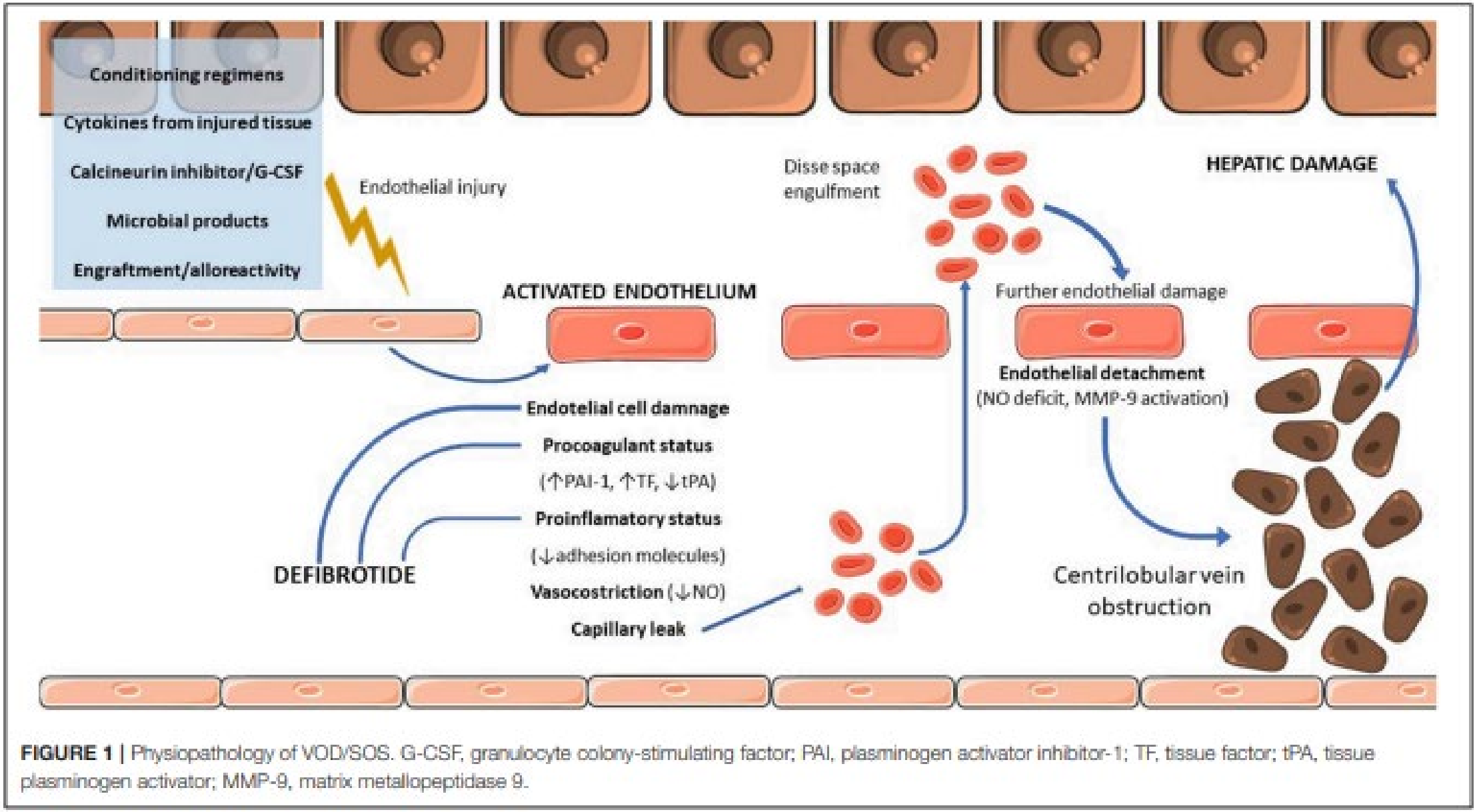


FIGURE 1 | Physiopathology of VOD/SOS. G-CSF, granulocyte colony-stimulating factor; PAI, plasminogen activator inhibitor-1; TF, tissue factor; tPA, tissue plasminogen activator; MMP-9, matrix metallopeptidase 9.

Bonifazi F et al. Front Immunol. 2020 Apr 3;11:489

Biology of Blood and Marrow Transplantation

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GI	Variable apoptotic criteria (≥1/piece) in crypts	Destruction of glands, ulceration or submucosal fibrosis may reflect severe or long-standing disease but are not specific for chronic GVHD
Skin, in general	Apoptosis in epidermal basal layer or	

- GVHD of the liver affects 8–9% of all allogeneic HSCT recipients, **mostly occurring in conjunction with gut involvement**.
- **The liver is the most difficult of the GVHD-targeted organs** to assess because of the relative non-specificity of the laboratory findings, the co-existence of infection, and/or potential overlap with drug-induced liver injury (DILI).
- **Damage or destruction of the small bile ducts, ductitis, cholestasis, and variable inflammation are the hallmarks of liver GVHD.**

H.M. Shulman et al. Biol Blood Marrow Transplant 21 (2015) 589-603

In: Yeung, C., Shulman, H. (eds) 2019 Pathology of Graft vs. Host Disease. Springer, Cham.

Injury depends on:

- duration of hepatic GVHD
- therapeutic intervention, which may precede biopsy.

Refractory GVHD in the liver:

- **chronic cholestasis**, ductopenia
- less commonly, a ductular reaction response, unlike other chronic cholestatic liver diseases.
- A ductular reaction may be present with concomitant gut GVHD or **septicemia**, (cholangitis lenta)

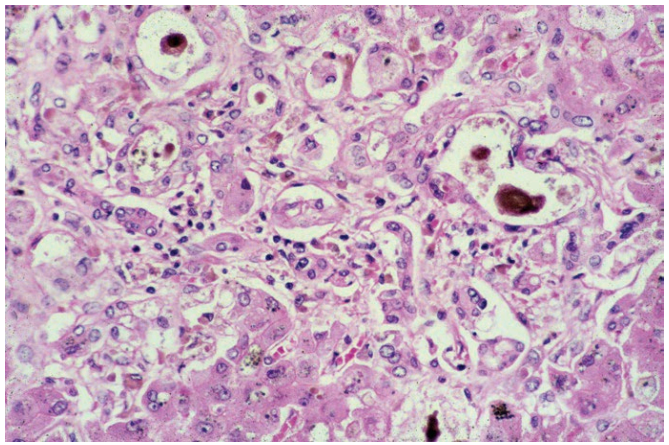
A Coded Histologic Study of Hepatic Graft-Versus-Host Disease after Human Bone Marrow Transplantation

HOWARD M. SHULMAN, PANKAJ SHARMA, DEBORAH AMOS, L. FREDERICK FENSTER AND GEORGE B. MCDONALD

TABLE 3. Relationships of histologic features to duration of GVHD

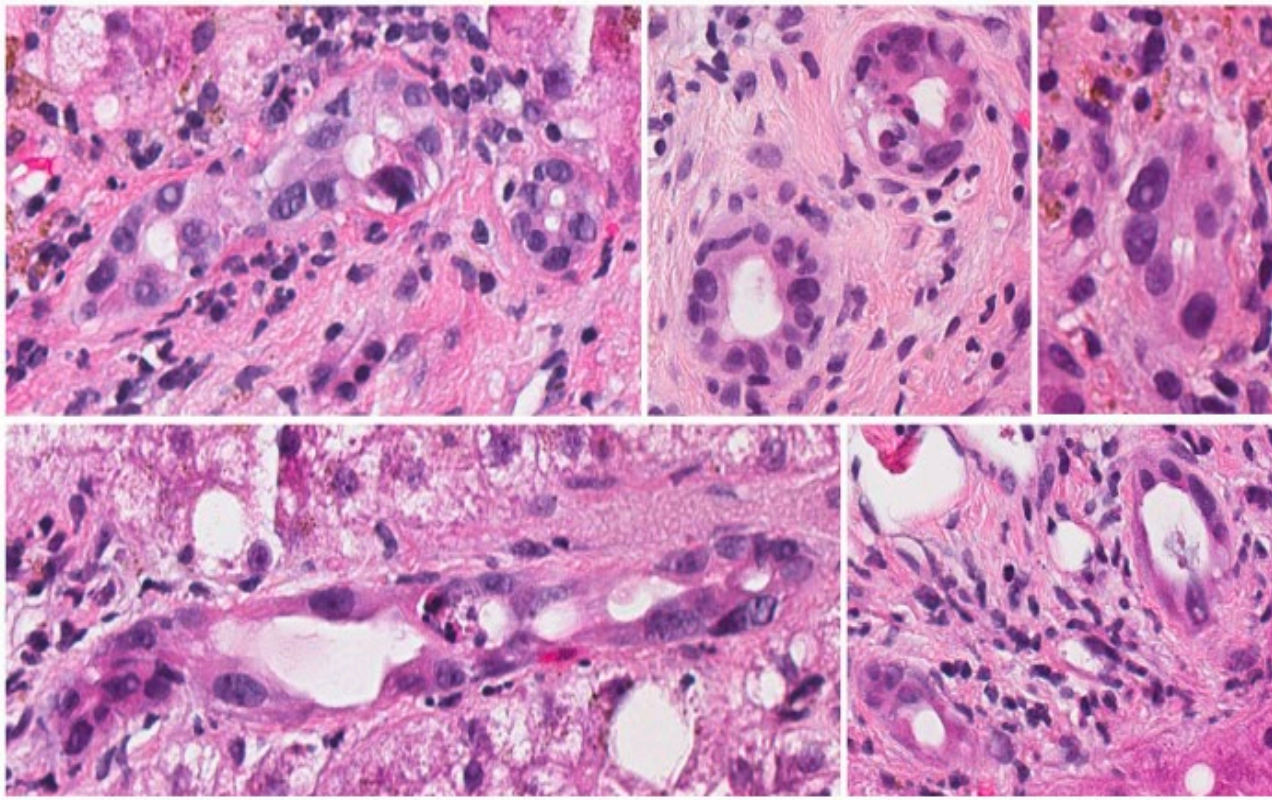
Feature	Significance level 3-Way test[a] (p)	GVHD period where feature is seen more frequently
Acidophilic bodies	0.06	Acute
Bile duct exocytosis	0.01	Prolonged
Bile duct disruption of epithelial cells	0.11	Prolonged
Bile duct dropout	0.04	Chronic
Portal expansion	0.02	Chronic
Portal fibrosis	0.12	Chronic

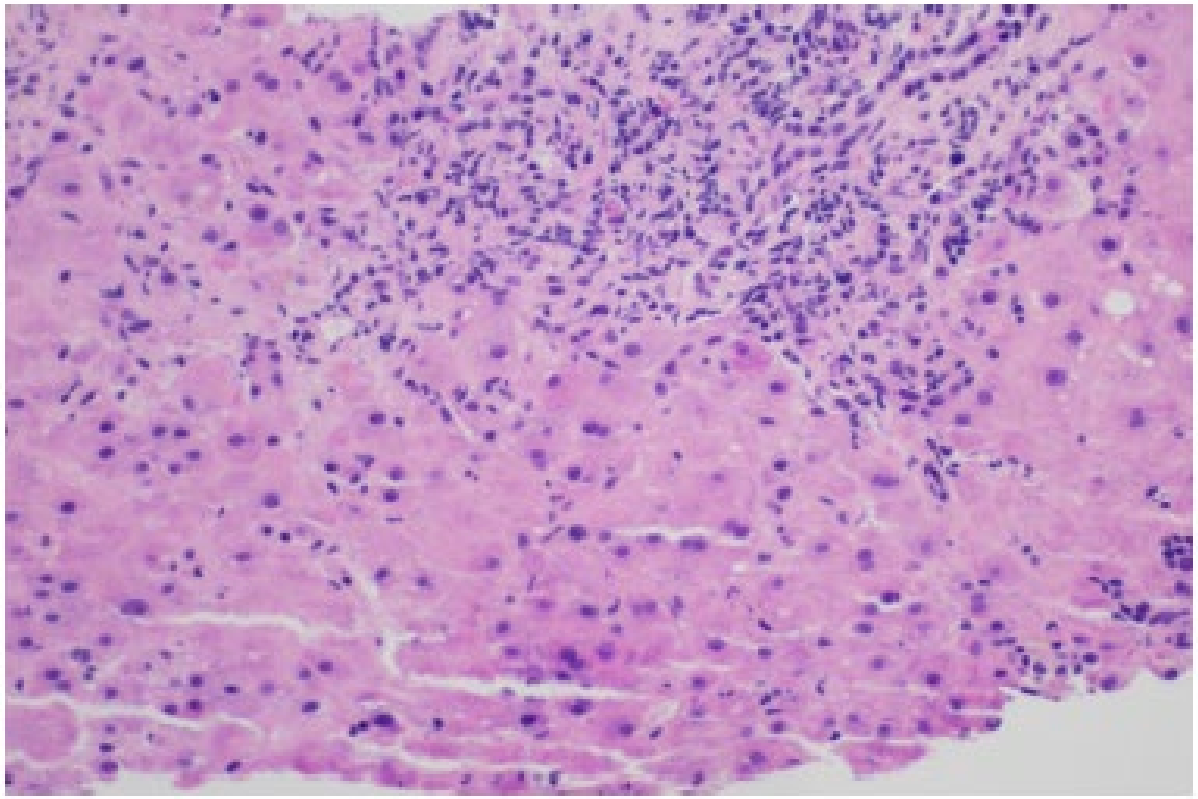
[a] 3-way test: acute, <Day 35; prolonged, Days 35–90; chronic, >Day 90.



Shulman et al, Hepatology, Vol. 8, No. 3, pp. 463-470, 1988

Classical GvHD vs hepatitic GvHD





Stueck AE et al, Human Pathology (2023) 141, 170-182

Hepatitic graft versus host disease

- **Histopathologic changes do not correlate with the clinical time-based distinction of acute and chronic GVHD**
- No histologic grading system currently exists
- Two histologic patterns are seen: hepatitic and classical.
- The hepatitic pattern of hGVHD is seen in a minority of cases and is typically associated with ALT and AST elevation, occasionally >10 ULN.
- more frequent at <100 days post-HCT, during tapering of immunosuppression, and after donor lymphocyte infusions
- Lymphocyte-rich, but can resemble autoimmune hepatitis (autoantibodies!)
- *Isolated hepatic GVHD has been reported in approximately **1%** of cases, 3 weeks-3 months following BMT with jaundice and hepatomegaly. Laboratory testing may show elevated serum alkaline phosphatase and bilirubin with or without transaminitis.*

https://www.aasld.org/liver-fellow-network/core-series/pathology-pearls/pathology-pearls-graft-versus-host-disease-gvhd-0

Hepatitic variant of graft-versus-host disease after donor lymphocyte infusion

Görgün Akpek, John K. Boitnott, Linda A. Lee, Jason P. Hallick, Michael Torbenson, David A. Jacobsohn, Sally Arai, Viki Anders, and Georgia B. Vogelsang

OR TAPERING OF STEROIDS

- Liver GVHD developed after DLI in 22 (30%) patients
- median age was 43 years (range, 21 to 61 years)
- Onset of liver dysfunction was at 35 days (range, 11 to 406 days) after DLI

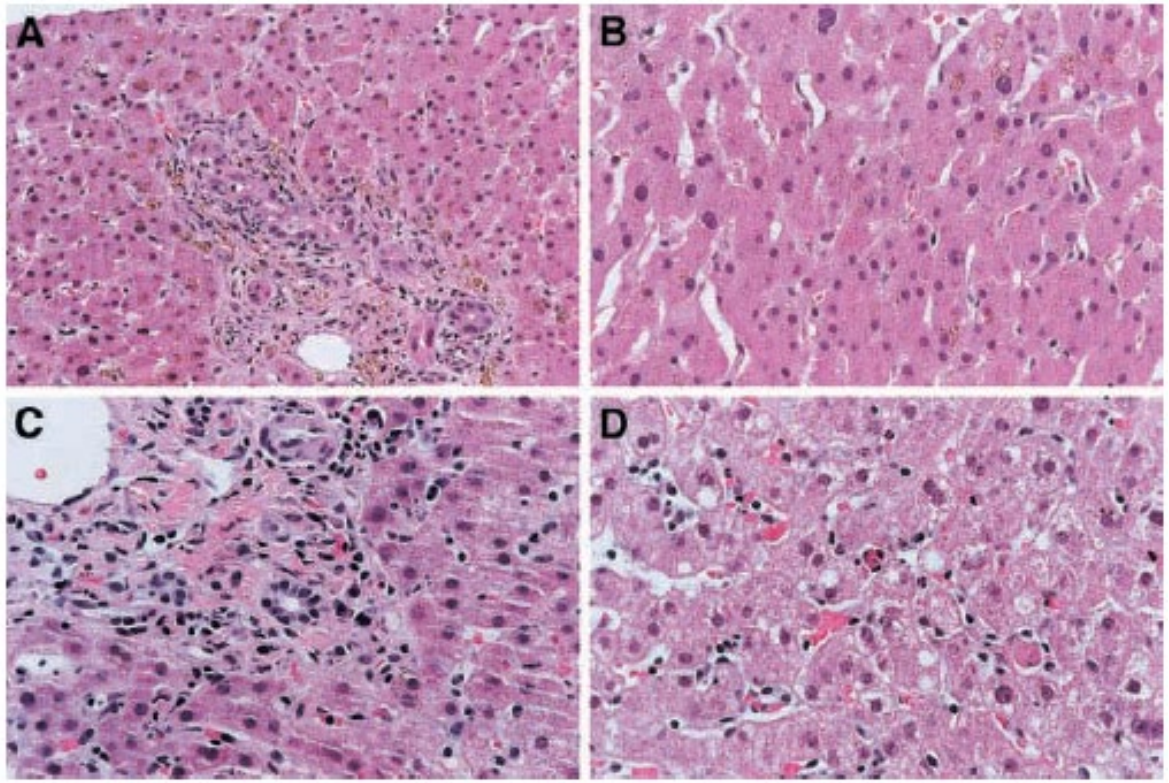
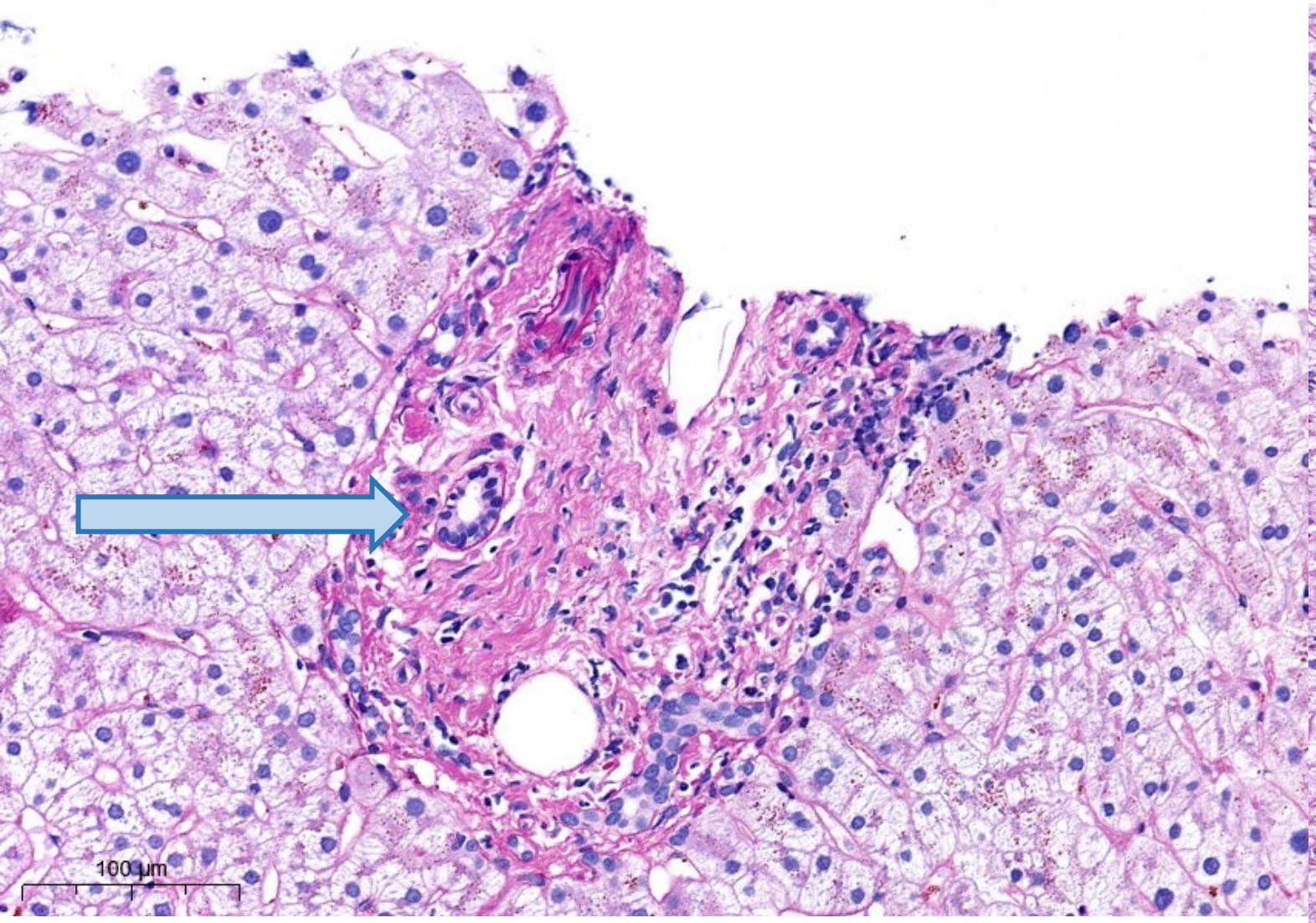
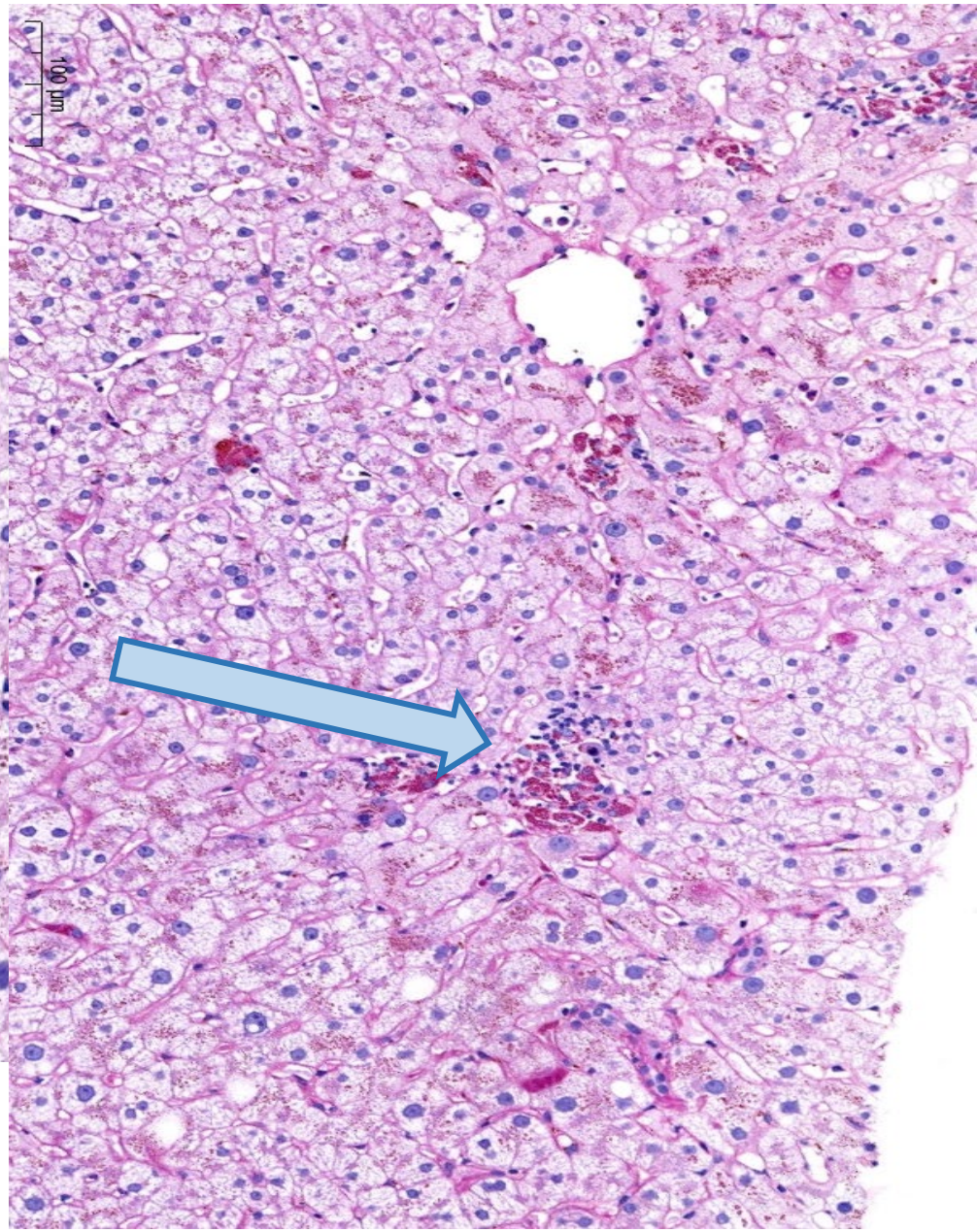


Table 4. Comparison of serum liver enzymes between classical and hepatitic liver GVHD

	Median (10th percentile, 90th percentile)		
	Classical liver GVHD n = 11	Hepatitic-variant GVHD n = 11	*P*
Alkaline phosphatase	542 (271, 1980)	362 (158, 1262)	NS
ALT	315 (142, 411)	825 (318, 1495)	.002
AST	190 (78, 289)	383 (226, 918)	.01
Total bilirubin	5.1 (0.5, 31.9)	2.6 (1.0, 18.4)	NS
Direct bilirubin	2.1 (0.2, 26.3)	1.4 (0.3, 6.9)	NS

Akpek G et al, Blood 2002; 100:3903-3907

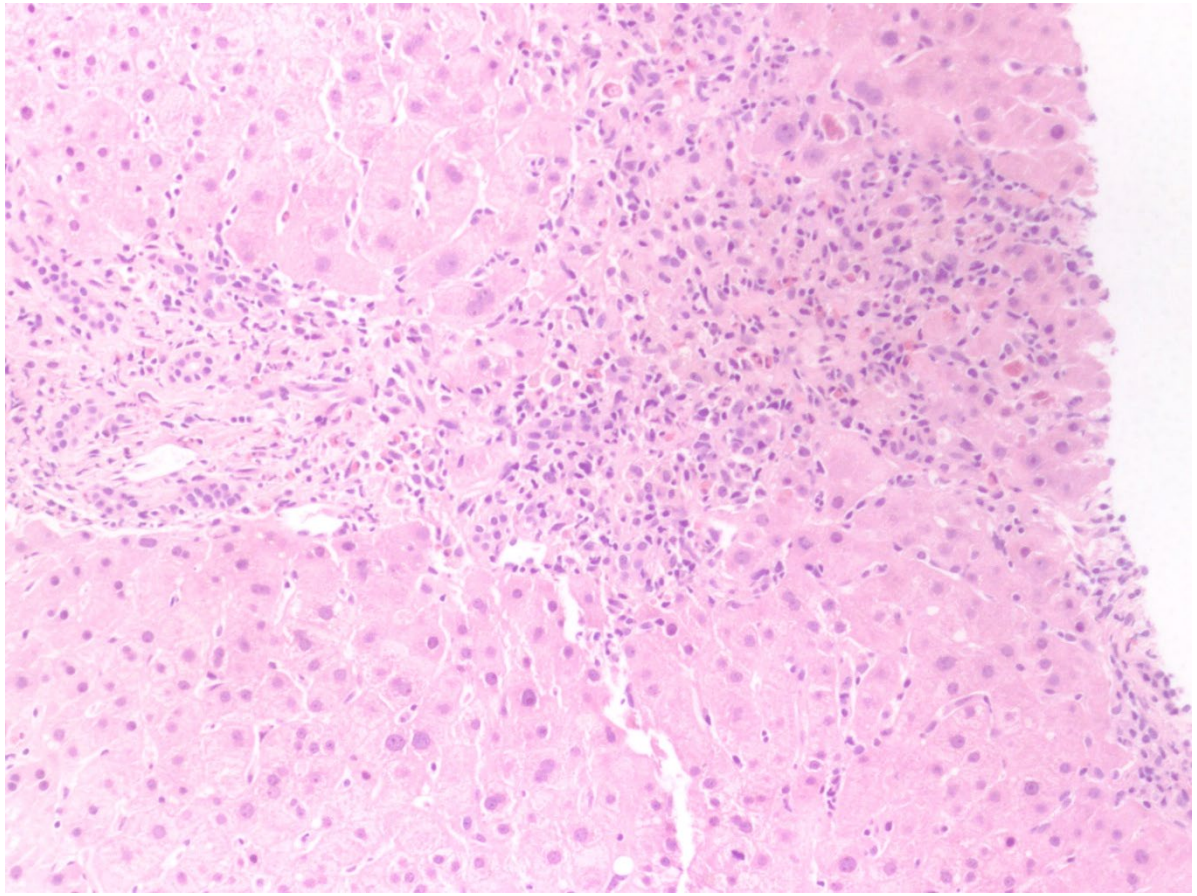


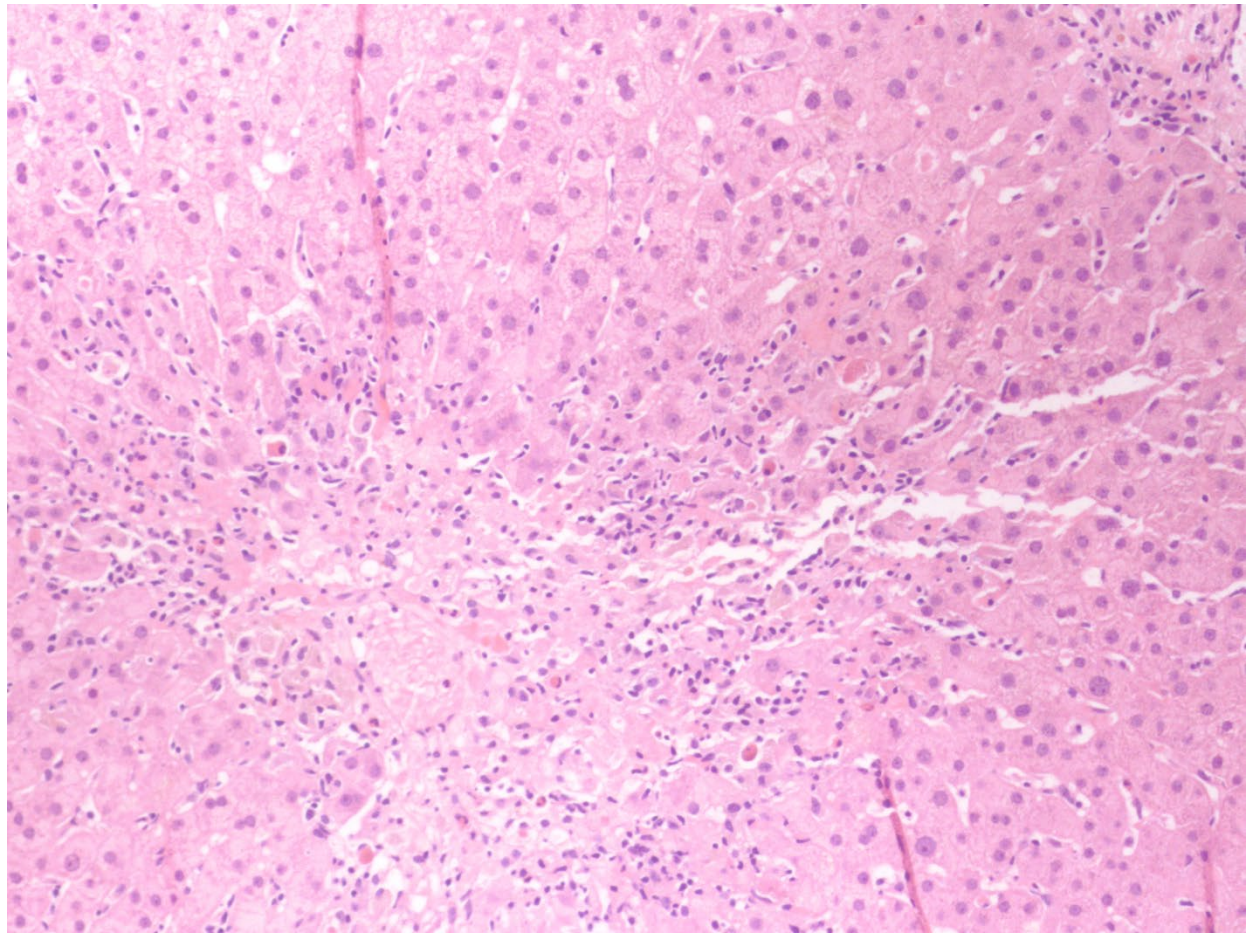


PAS-D

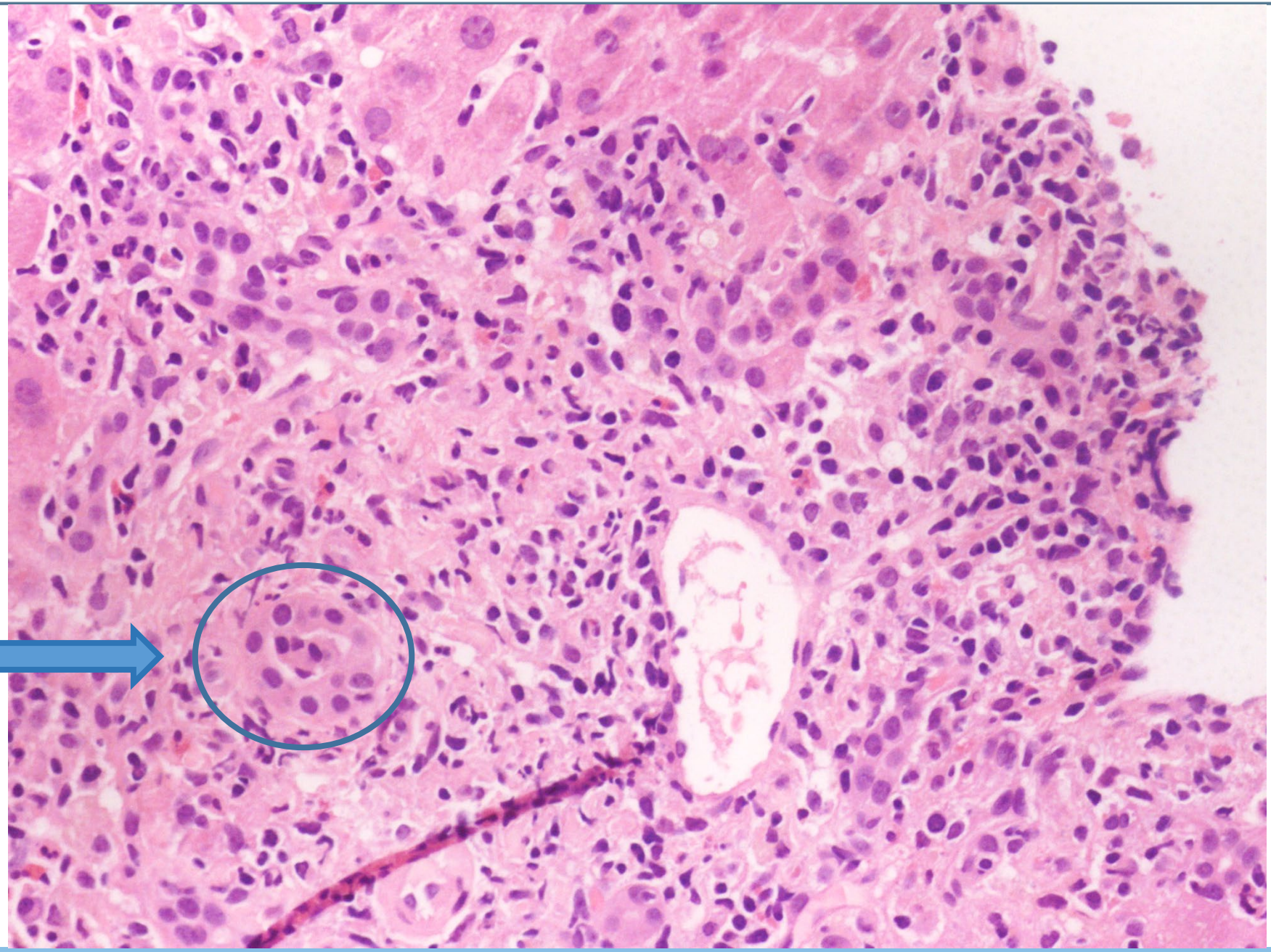
A.A., 60 ys old, allogenic BMT on May 29th for AML

- Chemotherapy induced toxidermia
- aGVHD skin BMT+9
- HHV6 reactivation (44,000 copies) and CMV reactivation
- Increased cholestasis and liver necrosis indices in October 2024: start of cyclosporine + steroid, liver needle biopsy
- eosinophilia





Thanks to Dr.ssa Vera Radici (Spedali Civili di Brescia)



Differential Diagnosis of Liver Graft-vs-Host Disease

- Infections
  - Viral hepatitis A, B, C, E
  - Systemic viral illness (eg, CMV, HSV, HHV6, EBV)
  - Bacterial, fungal (rare)
- Medications (methotrexate, cyclosporine, other chemotherapy)
- Sinusoidal obstruction syndrome
- Biliary tract disease
- Hepatic iron overload

And autoimmune liver disease

Often found in BMT patients

Checkpoint inhibitor!

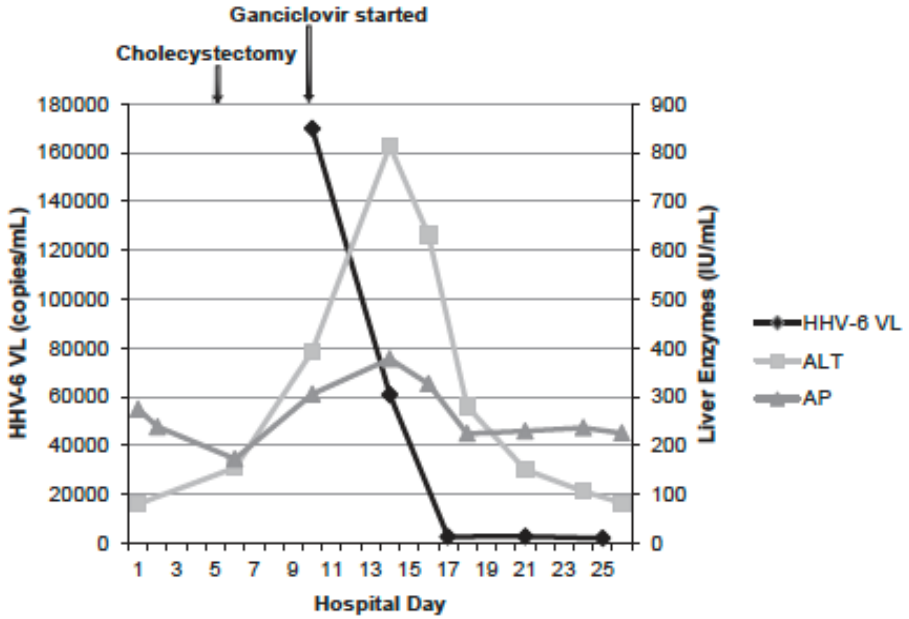
CAR-T toxicity

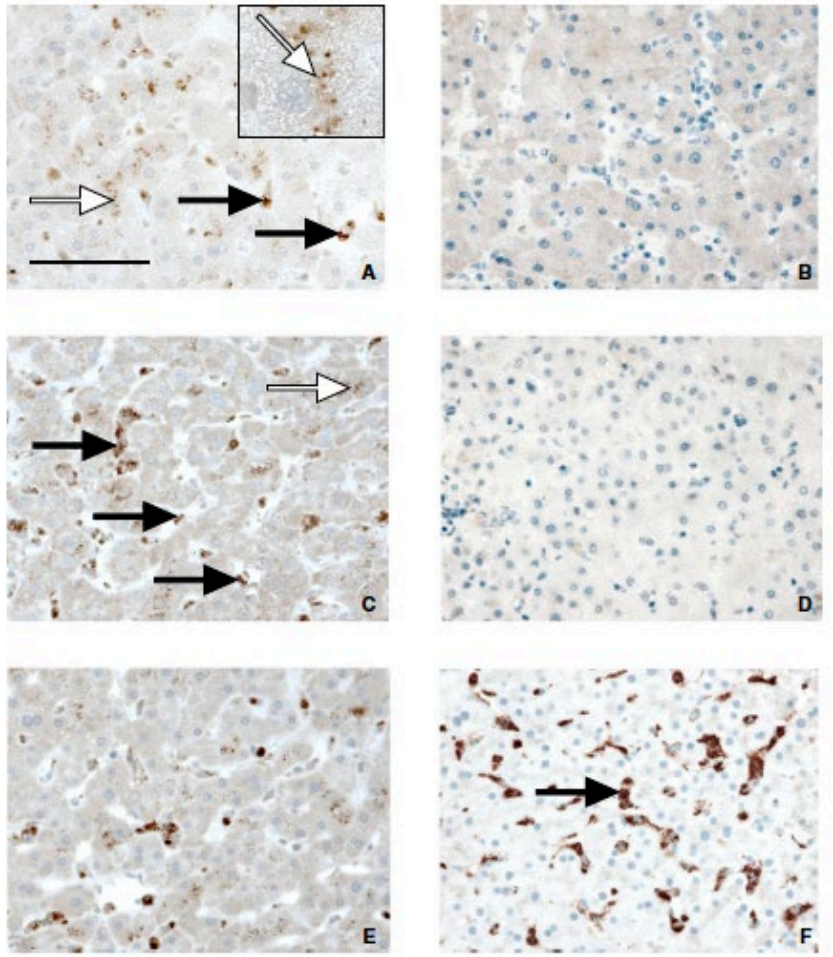
CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV6, human herpesvirus 6; HSV, herpes simplex virus.

Salomao M et al, Am J Clin Pathol 2016;145:591-603

Human Herpes Virus 6

- 33% to 48% of alloSCT recipients experience HHV-6 reactivation
- 2 to 4 weeks after alloSCT associated with hepatitis, pneumonitis, CMV reactivation, fever and rash, myelosuppression, and encephalitis





- Liver biopsy demonstrated slight abnormalities of the bile ductules and proliferation of the larger bile ducts.
- Occasional neutrophilic aggregates were seen, indicative of lobular hepatitis.
- Very rare apoptotic hepatocytes were present.
- The trichrome stain showed no evidence of sinusoidal obstruction syndrome

Hill JA et al, Transplant Infectious Disease 2014: 16: 477–483

Guidelines from the 2017 European Conference on Infections in Leukaemia for management of HHV-6 infection in patients with hematologic malignancies and after hematopoietic stem cell transplantation

Katherine N Ward,[1] Joshua A Hill,[2] Petr Hubacek,[3] Rafael de la Camara,[4] Roberto Crocchiolo,[5] Hermann Einsele,[6] David Navarro,[7] Christine Robin,[8] Catherine Cordonnier,[8] and Per Ljungman;[9] for the 2017 European Conference on Infections in Leukaemia (ECIL)*

Table 4. Human herpesvirus 6B reactivation after allogeneic hematopoietic stem cell transplantation: disease associations.

Epidemiological associations	Level of *in vitro* or *in vivo* support for causation
HHV-6B end-organ disease	
Encephalitis (predominantly limbic)	Strong
Non-encephalitic central nervous system dysfunction e.g. delirium, myelitis	Moderate
Myelosuppression, allograft failure	Moderate
Pneumonitis	Weak
Hepatitis	Weak
Other	
Fever and rash	Strong
Acute graft-*versus*-host disease	Moderate
CMV reactivation	Moderate
Increased all-cause mortality	Weak

HHV-6B: human herpesvirus 6B; CMV: cytomegalovirus. Adapted from Table 29.2 in Hill and Zerr.[86]

Biol Blood Marrow Transplant 22 (2016) 2250–2255

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Human Herpesvirus 6 Infection Following Haploidentical Transplantation: Immune Recovery and Outcome

Raffaella Greco [1], Lara Crucitti [2], Maddalena Noviello [3], Sara Racca [4], Daniele Mannina [1], Alessandra Forcina [1], Francesca Lorentino [1], Veronica Valtolina [3], Serena Rolla [4], Roee Dvir [4], Mara Morelli [1], Fabio Giglio [1], Maria Chiara Barbanti [1], Maria Teresa Lupo Stanghellini [1], Chiara Oltolini [5], Luca Vago [1,6], Paolo Scarpellini [5], Andrea Assanelli [1], Matteo G. Carrabba [1], Sarah Marktel [1], Massimo Bernardi [1], Consuelo Corti [1], Massimo Clementi [4,7], Jacopo Peccatori [1], Chiara Bonini [3], Fabio Ciceri [1,7,*]

ASBMT American Society for Blood and Marrow Transplantation

BRIEF ARTICLES

The Complex Relationship between Human Herpesvirus 6 and Acute Graft-versus-Host Disease

Claire Pichereau,[1] Kristell Desseaux,[2] Anne Janin,[3,4,5] Catherine Scieux,[3,6] Régis Peffault de Latour,[1,3] Aliénor Xhaard,[1,3] Marie Robin,[1] Patricia Ribaud,[1,3] Félix Agbalika,[3,6] Sylvie Chevret,[2,3,7] Gérard Socié[1,3,4]

The most frequent manifestation of human herpesvirus 6 (HHV-6) reactivation after allogeneic hematopoietic stem cell transplantation (HSCT) is febrile rash, raising the question of its relationship with graft-versus-host disease (GVHD). In this retrospective analysis of 365 patients who underwent allogeneic HSCT, HHV-6 reactivation was significantly associated with cord blood transplantation (hazard ratio [HR], 3.20; $P < .0001$) and the use of unrelated donors (HR, 2.02; $P = .008$). On multivariate analysis, previous GVHD was a predictive factor for HHV-6 reactivation (HR, 1.80; $P = .01$), and previous HHV-6 reactivation was a predictive factor for acute GVHD (HR, 1.66; $P = .03$). Nineteen patients with no pathological evidence of GVHD later developed severe clinical GVHD (grade III-IV), suggesting the role of HHV-6 as a trigger for severe GVHD. Furthermore, 17 patients without histopathological GVHD demonstrated a significant lymphoid infiltrate suggesting "pure" HHV-6–related manifestations, and these patients could have been spared steroid therapy.

Biol Blood Marrow Transplant 18: 141-144 (2012) © 2012 American Society for Blood and Marrow Transplantation

KEY WORDS: Transplantation, GvHD, Human, GvHD diagnosis

- *median time to HHV-6 reactivation was 34 days after alloSCT*
- *29/54 patients developed acute GvHD, after HHV6 reactivation*
- *15 concomitant CMV reactivation*

- previous GVHD was a predictive factor for HHV-6 reactivation
- previous HHV-6 reactivation was a predictive factor for acute GVHD

Citomegalovirus

- 32 transplant recipients with CMV infection documented by positive culture of blood and/or organs other than the liver were evaluated for hepatic involvement.
- 41% hepatic involvement with CMV.
- Inclusions alone were present in three patients; liver cultures alone were positive for CMV in three; and both were present in seven.
- lobular aggregates of polymorphonuclear cells and portal karyorrhexic debris (for diagnosis)
- The presence of liver involvement had a significant correlation with multiple organ infection, indicating it is a *good marker of widely disseminated disease*.
- This study indicates that liver histology and culture are useful and complementary methods for documentation of hepatic involvement (hence, tissue invasion) in immunocompromised patients with CMV infection.

Snover DC et al, J Clin Gastroenterol. 1987;9(6):659–65.

Evidence for a Bidirectional Relationship between Cytomegalovirus Replication and acute Graft-versus-Host Disease

Nathan Cantoni,[1] Hans H. Hirsch,[2,3] Nina Khanna,[2,3] Sabine Gerull,[1] Andreas Buser,[1] Christoph Bucher,[1] Jörg Halter,[1] Dominik Heim,[1] André Tichelli,[1] Alois Gratwohl,[1] Martin Stern[1]

Cantoni N et al. Biol Blood Marrow Transplant 16: 1309-1314 (2010)

Clinical pattern of checkpoint inhibitor-induced liver injury in a multicentre cohort

Authors
Lina Hountondji, **Christophe Ferreira De Matos**, Fanny Lebossé, Xavier Quantin, Candice Lesage, Pascale Palassin, Valérian Rivet, Stéphanie Faure, Georges-Philippe Pageaux, Éric Assenat, Laurent Alric, Amel Zahhaf, Dominique Larrey, Philine Witkowski Durand Viel, Benjamin Riviere, Selves Janick, Stéphane Dalle, Alexandre Thibault Jacques Maria, Thibaut Comont, Lucy Meunier

CHeckpoint Inhibitor-induced Liver Injury (CHILI): A multicenter cohort of 117 patients

POPULATION

n = 117 patients
CHeckpoint Inhibitor-induced Liver Injury

Age: 63 years old
Male: 53.8%

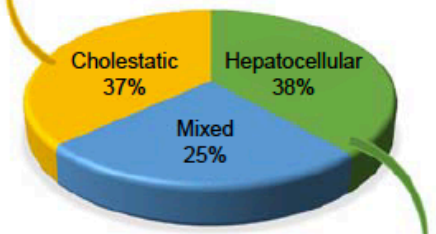
82% Grade 3 or 4

Anti-PD(L)1 60%	Anti-PD(L)1 + anti-CTLA-4 36%
Anti-CTLA-4 3%	Anti-PD(L)1 + anti-LAG-3 1%

HEPATITIS

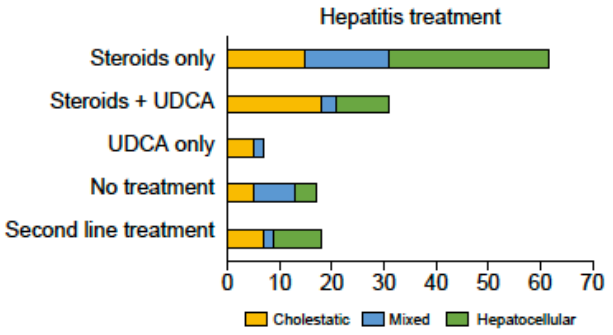
Anti-PD(L)-1
Bile duct injury
Histology: biliary injury

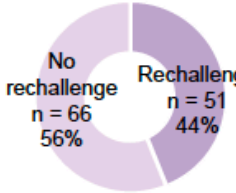
Clinical pattern



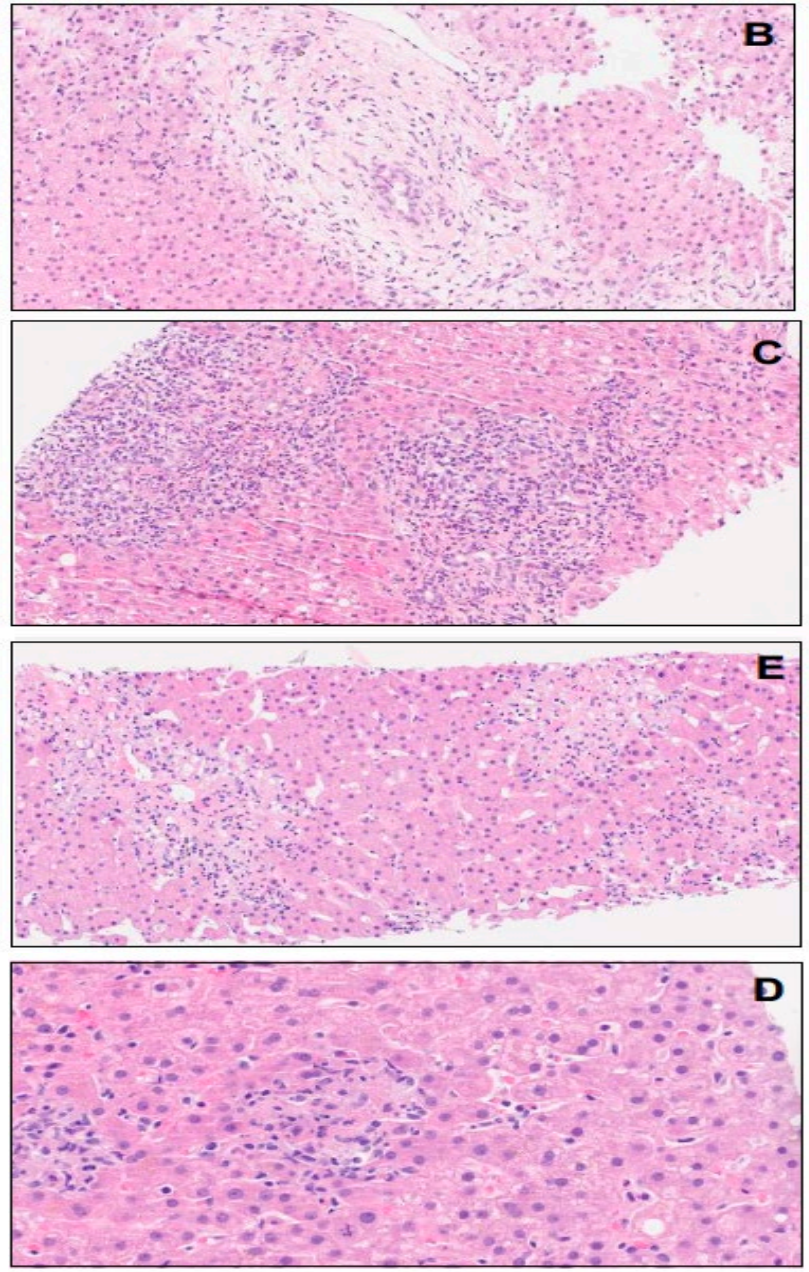
Anti-CTLA-4 + anti-PD-1

TREATMENT & RECHALLENGE





Hepatitis recurrence
n = 12
23.5%

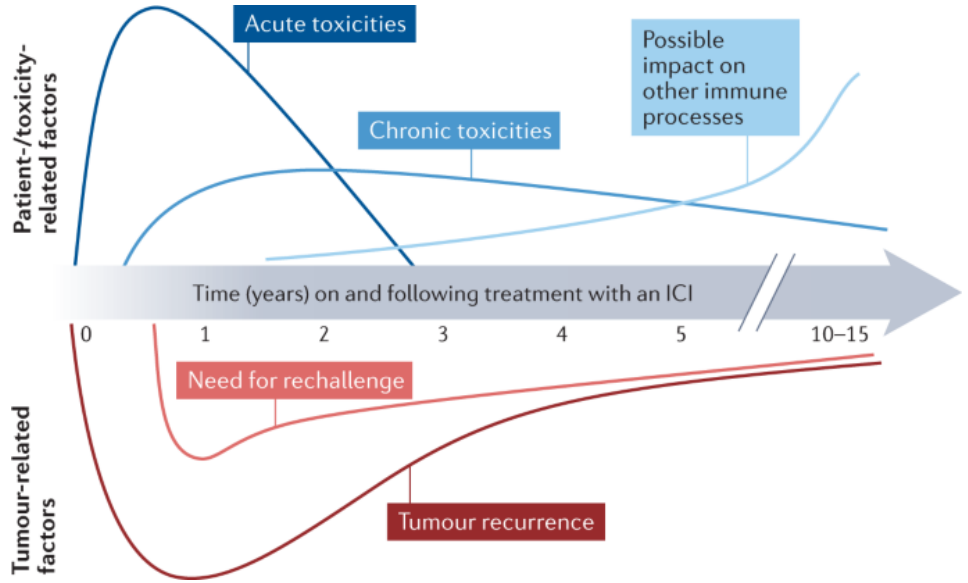


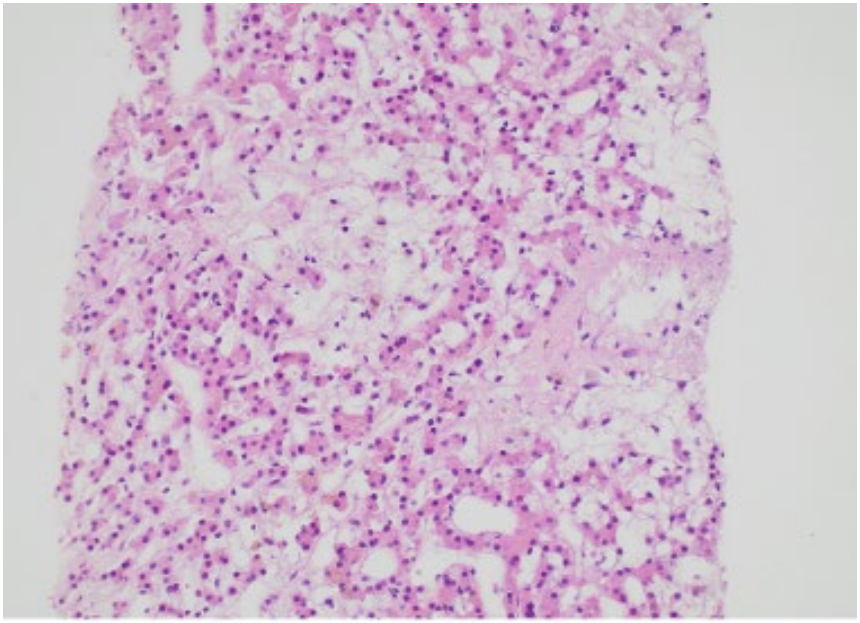
Pembrolizumab-Induced Liver Injury: Beyond Immune-Mediated Hepatitis

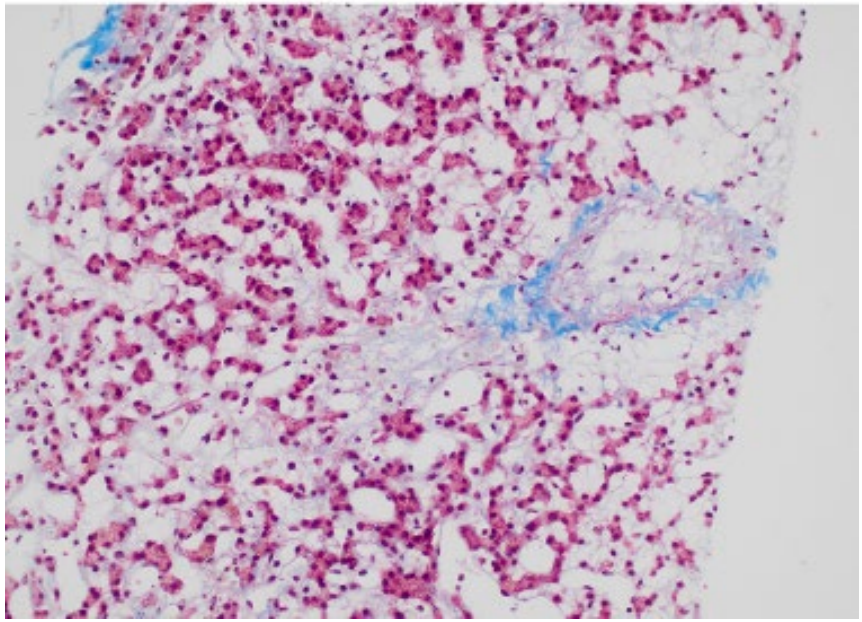
Queralt Herms,[1] Carla Fuster-Anglada,[2,3,4] and Adrià Juanola[1,3,4]

[1]Liver Unit, Hospital Clinic de Barcelona, Barcelona, Spain; [2]Department of Pathology, Hospital Clínic de Barcelona, Universitat de Barcelona, Barcelona, Spain; [3]Institut d'Investigacions Biomediques August Pi i Sunyer, Barcelona, Spain; and [4]Centro de Investigacion Biomedica en Red Enfermedades Hepaticas y Digestivas, Barcelona, Spain

…no previous reports of SOS associated with pembrolizumab treatment have been reported. The present patient had no other identifiable cause of SOS except for pembrolizumab treatment during the previous 9 months of onset of ascites. Therefore, SOS might be linked to the PD-1 inhibitor pembrolizumab, expanding the range of adverse events related to this drug…



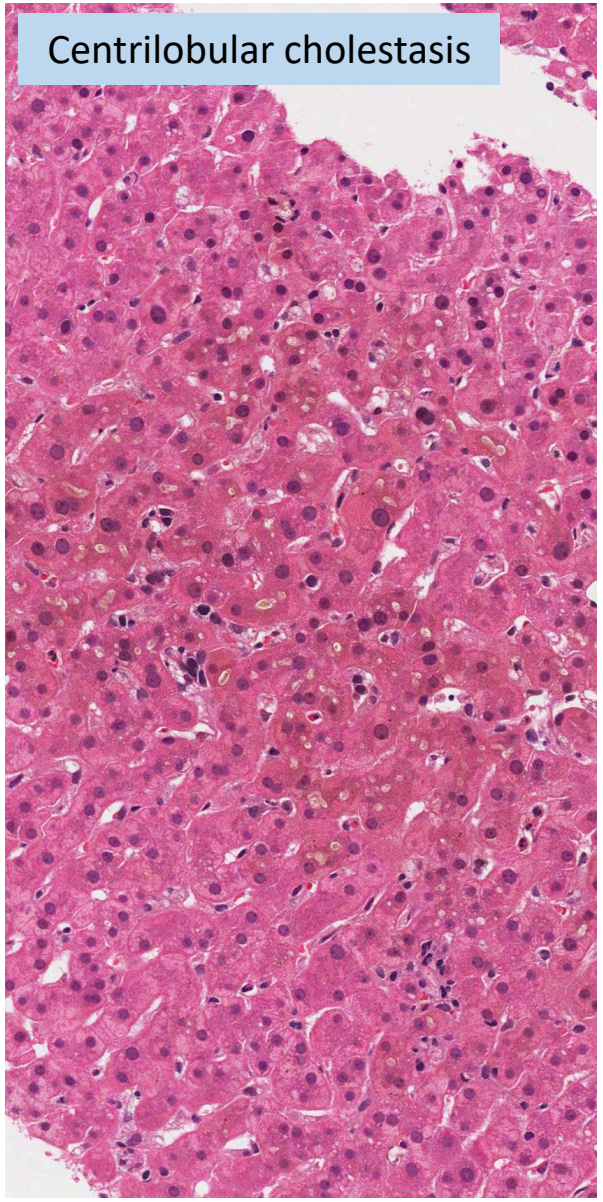


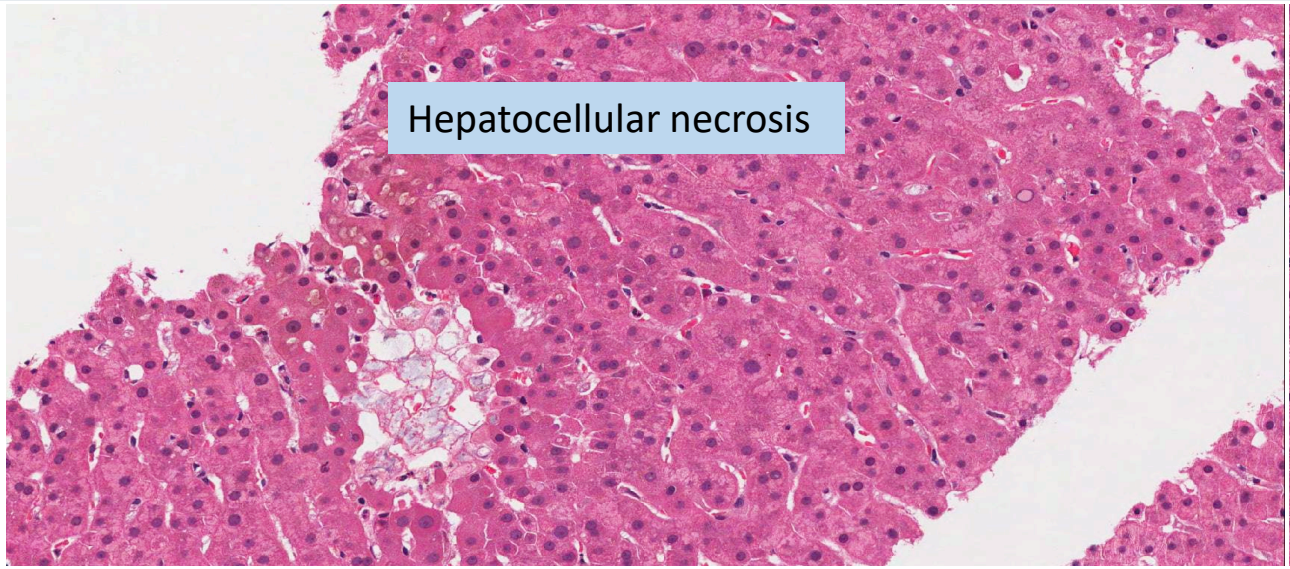


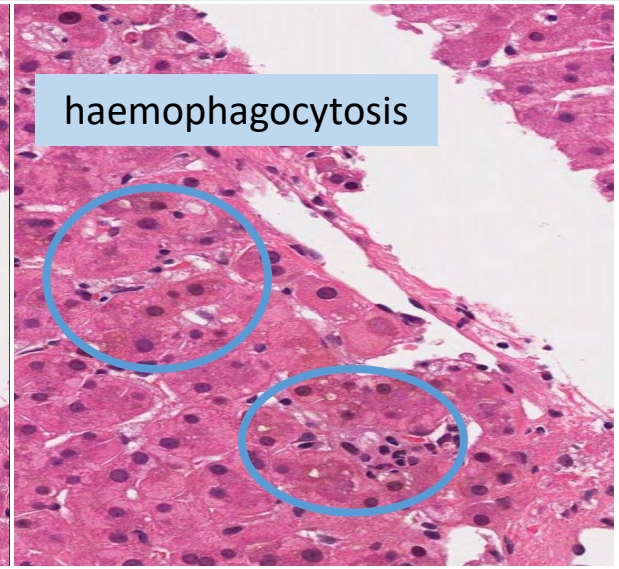
Johnson DB et al, Nat Rev Clin Oncol 2022; **19**, 254–267

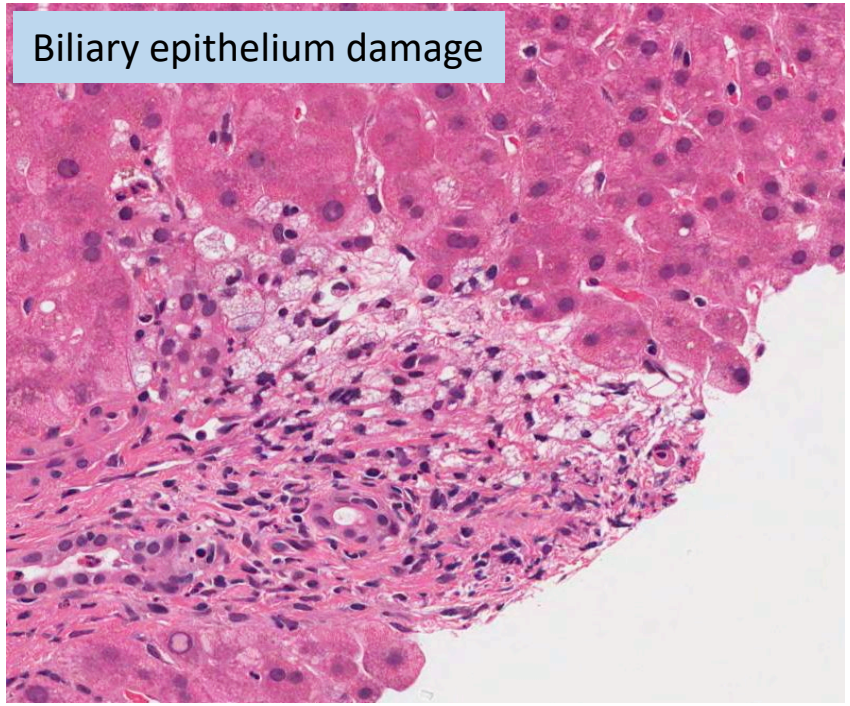
Herms Q et al, Gastroenterology 2024;167:443–445

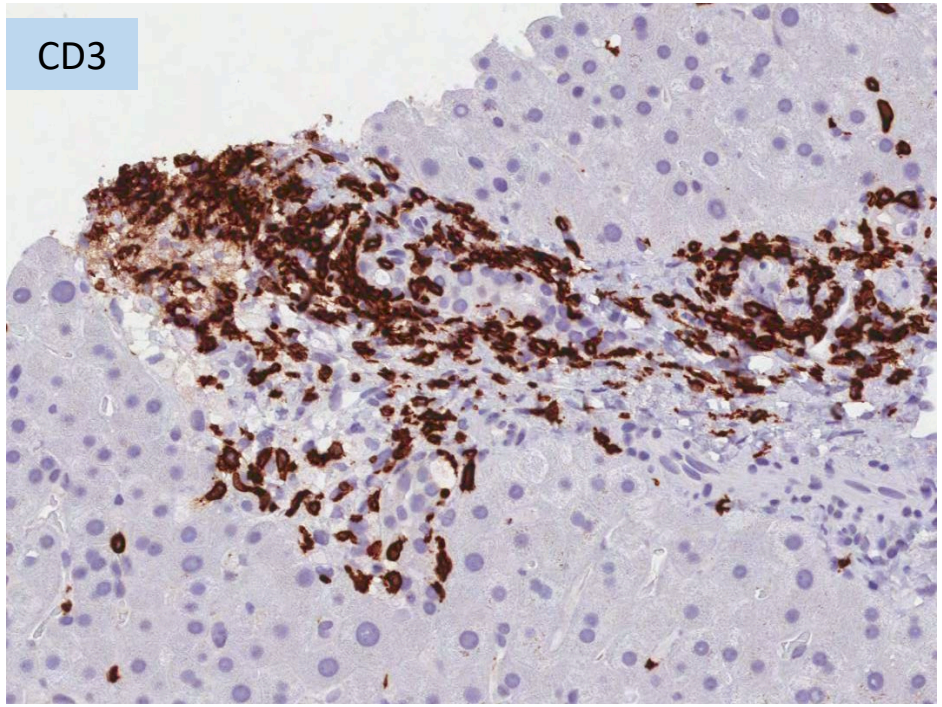
CAR-T toxicity











Acute Graft-Versus-Host Disease After Humanized Anti-CD19-CAR T Therapy in Relapsed B-ALL Patients After Allogeneic Hematopoietic Stem Cell Transplant

Pengjiang Liu[1], Meijing Liu[2], Cuicui Lyu[1], Wenyi Lu[1], Rui Cui[1], Jia Wang[1], Qing Li[1], Nan Mou[3], Qi Deng[1] and Donglin Yang[4]**

TABLE 2 | The therapeutic effect, donor chimerism analysis, and acute GVHD after anti-CD19-CAR T-cell therapy.

Patient	Donor Type	CR/Cri	MRD	Donor chimerism (%)	Time of aGVHD (Days after CAR-T therapy)	Grade of aGVHD	Site of aGVHD	Therapy to aGVHD
Pt 1#	MMUDT (8/10)	Cri	Negative	99.86	60–102	II	S2, G1	Glucocorticoid, CsA
Pt 2#	MSDT	CR	Negative	99.83	35–97	I	S2	Glucocorticoid
Pt 3#	Haplo-HSCT (7/10)	CR	Negative	99.92	32–77	II	G1	Glucocorticoid
Pt 4#	Haplo-HSCT (5/10)	Cri	Negative	99.86	52–64	III	L3	Glucocorticoid, CsA, Anti-CD25 monoclonal antibody
Pt 5#	Haplo-HSCT (5/10)	Cri	Negative	99.91	24–104	IV	S3, L2, G4	Glucocorticoid, CsA, Ruxolitinib
Pt 6#	MUDT	NR	Positive	10.72	0	0	-	-
Pt 7#	Haplo-HSCT (5/10)	CR	Negative	99.94	0	0	-	-
Pt 8#	MSDT	CR	Positive	99.94	51–93	I	S1	Glucocorticoid
Pt 9#	Haplo-HSCT (5/10)	CR	Negative	99.94	0	0	-	-
Pt 10#	MSDT	Cri	Positive	99.77	0	0	-	-
Pt 11#	MSDT	CR	Negative	99.66	42–74	I	S1	Glucocorticoid
Pt 12#	Haplo-HSCT (5/10)	Cri	Negative	99.91	0	0	-	-
Pt 13#	Haplo-HSCT (5/10)	NR	Positive	99.56	31–102	III	S3, G3	Glucocorticoid, CsA, Ruxolitinib
Pt 14#	Haplo-HSCT (5/10)	Cri	Negative	99.96	21–73	IV	S4, L2, G4	Glucocorticoid, CsA, Ruxolitinib
Pt 15#	Haplo-HSCT (5/10)	Cri	Negative	99.17	14–56	I	S1	Glucocorticoid

S, Skin; L, Liver; G, Gastrointestinal.

- Gastrointestinal 7
- Hepatic 1
- GI+hepatic 2

- aGVHD was observed in 10 of 15 patients (66.67%).
- 6 patients developed grade I-II of aGVHD, 4 patients developed grade III-IV of aGVHD.
- grade 1–2 cytokine release syndrome (CRS) in 10 patients and grade 3–4 CRS in five patients.
- Two patients died of infection, while another patient died of sudden cardiac arrest.
- The anti-CD19-CAR T cells were not eliminated in peripheral blood when the patients developed aGVHD.
- During the aGVHD, the peaks of IL-6 and TNF-a were correlated with aGVHD levels.

ARTICLE

IMMUNOTHERAPY

Graft-versus-host disease after anti-CD19 chimeric antigen receptor T-cell therapy following allogeneic hematopoietic cell transplantation: a transplant complications and paediatric diseases working parties joint EBMT study

Guillermo Ortí[1], Christophe Peczynski[2], William Boreland[2], Maeve O'Reilly[3], Malte von Bonin[4], Adriana Balduzzi[5,6], Caroline Besley[7], Krzysztof Kalwak[8], Samppa Ryhänen[9], Tayfun Güngör[10], Robert F. Wynn[11], Peter Bader[12], Stephan Mielke[13], Didier Blaise[14], Persis Amrolia[15], Ibrahim Yakoub-Agha[16], Friso Calkoen[17], Maria-Luisa Schubert[18], Victoria Potter[19], Herbert Pichler[20,21], Nicolaus Kröger[22], Mi Kwon[23], Henrik Sengeloev[24], Anna Torrent[25], Yves Chalandon[26], Gwendolyn van Gorkom[27], Christian Koenecke[28], Charlotte Graham[29], Helene Schoemans[30], Ivan Moiseev[31], Olaf Penack[32,33] and Zinaida Peric[34]

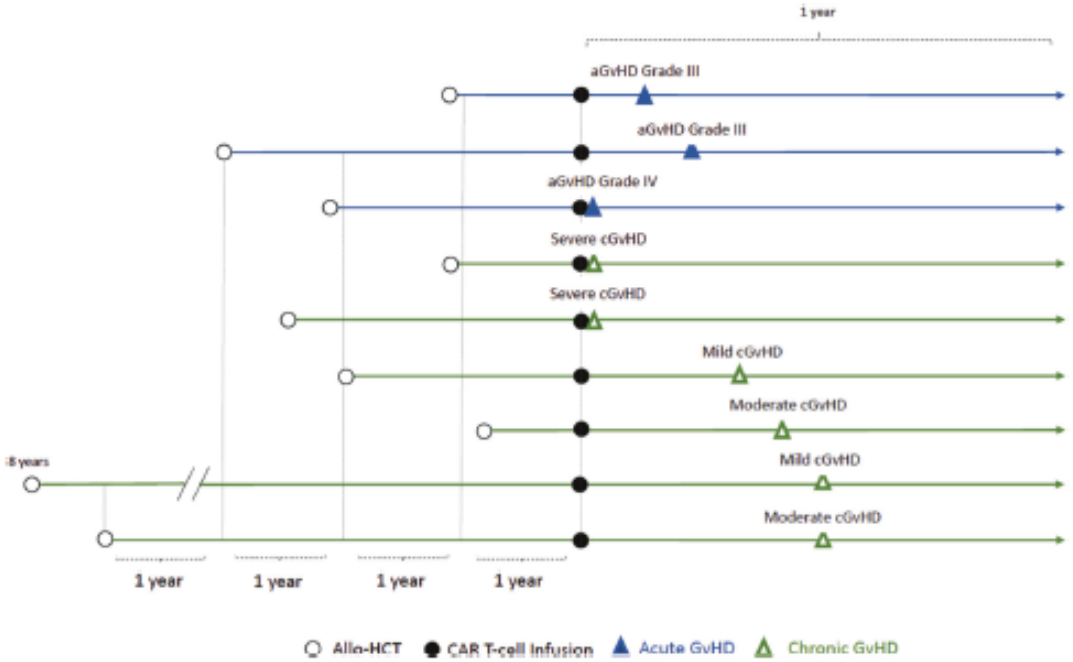


Table 2. **a** GvHD Score of patients developing acute GvHD after CAR T-cell therapy. **b** NIH GvHD Score of patients developing chronic GvHD after CAR T-cell therapy.

Patient	Time from allo-HCT to CAR T-cell (months)	Time from CAR T-cell to cGvHD (days)	aGvHD Score	Skin aGvHD Score	Lower GI Tract aGvHD Score	Liver cGvHD Score
1	10.3	46	Grade III	0	2	2
2	32.6	80	Grade III	1	2	0
3	12	8	Grade IV	2	4	1

Patient	Time from allo-HCT to CAR T-cell (months)	Time from CAR T-cell to cGvHD (days)	NIH Score	Skin cGvHD Score	Oral cGvHD Score	GI Tract cGvHD Score	Ocular cGvHD Score	Liver cGvHD Score	Joints & Fascia cGvHD Score	Lung cGvHD Score
1	5.6	37	Severe	1	0	1	0	3	0	0
2	6.8	5	Severe	3	3	0	0	0	0	3
3	24.3	119	Mild	1	0	0	0	0	0	0
4	6.9	167	Moderate	NA	NA	NA	NA	NA	NA	NA
5	99.5	178	Mild	0	1	0	0	0	0	0
6	54.9	166	Moderate	0	1	0	2	0	0	0

HCT hematopoietic cell transplant, *CAR* chimeric antigen receptor, *cGvHD* chronic graft-versus-host disease, *NA* not available, *GI* gastro-intestinal.

HCT hematopoietic cell transplant, *CAR* chimeric antigen receptor, *NIH* National Institute of Health, *cGvHD* chronic graft-versus-host disease, *NA* not available, *GI* gastro-intestinal.

Table 2
Recommendation for Final Diagnosis Categories

Category	Definition	Examples	Comments
Not GVHD	No evidence for GVHD		
Possible GVHD	Evidence of GVHD but other possible explanations	• Obvious CMV enteritis with inclusions near the apoptotic changes • Focal colonic ulcers with marked apoptotic cryptitis and destruction of crypts associated with use of MMF • Coinfection with known active viral hepatitis • Clinical features which suggest or favor a drug reaction	Indicate possible alternate diagnoses and reasons for suspicion
Likely GVHD	Clear evidence of GVHD without a competing cause of injury OR Clear evidence of GVHD with mitigating factors OR GVHD most likely diagnosis but relevant clinical information is limited OR GVHD is validated by sequential biopsy or by absence of competing diagnosis	• Abundant epithelial apoptosis without clinical or histological evidence of drug injury or infection • Evidence of CMV yet abundant apoptotic epithelial changes that are not associated with CMV infected cells by immunostaining • Single or rare apoptotic epithelial changes without other features of active GVHD and no alternative explanations • Limited sample or minimal or focal findings • Proximity to recent chemotherapy or radiotherapy	Included old categories of "consistent with" and "unequivocal" GVHD

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