Case #2

Timothy M. Bell, DO
Hematopathology Fellow, PGY-5

Cleveland Clinic

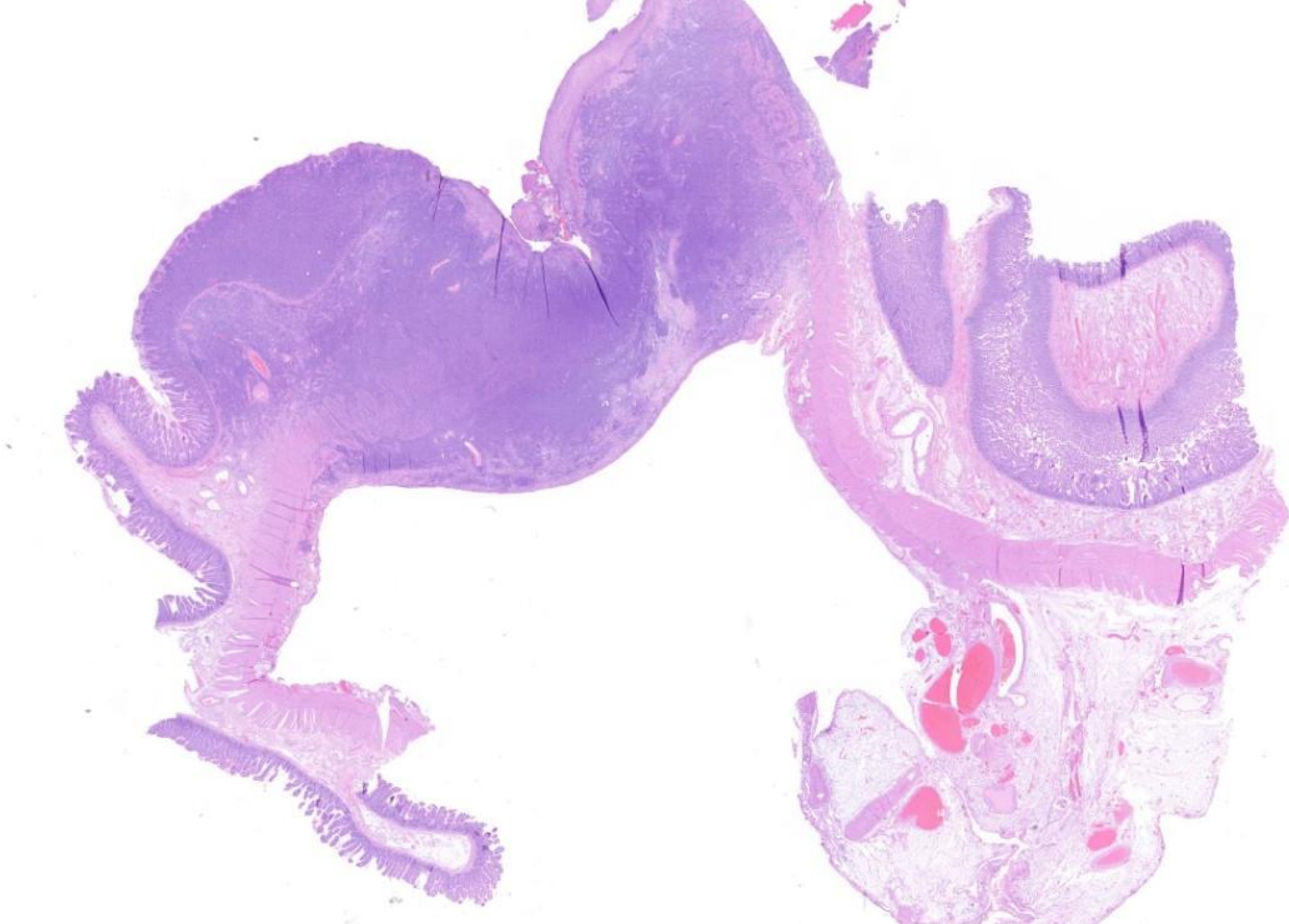
Case History

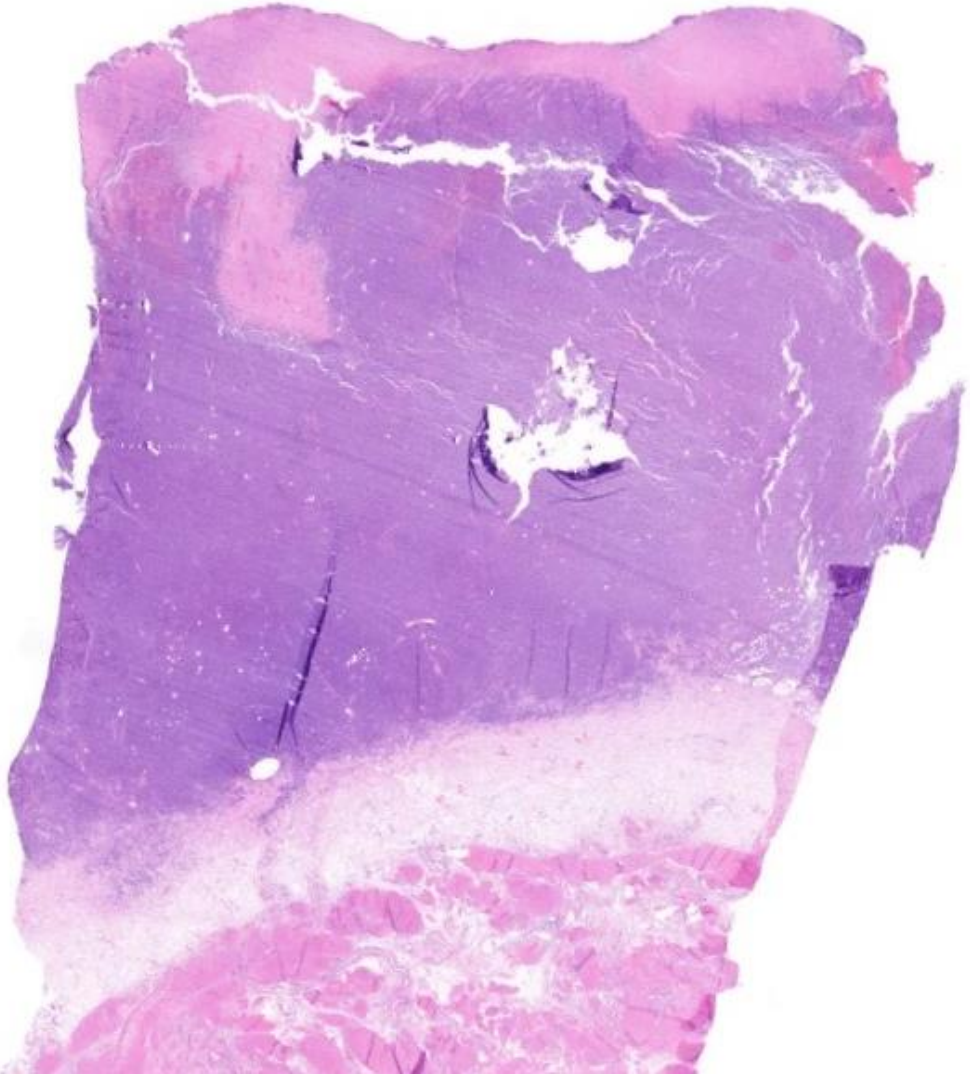
- 71-year-old male presented to the hospital with nausea and worsening abdominal pain.

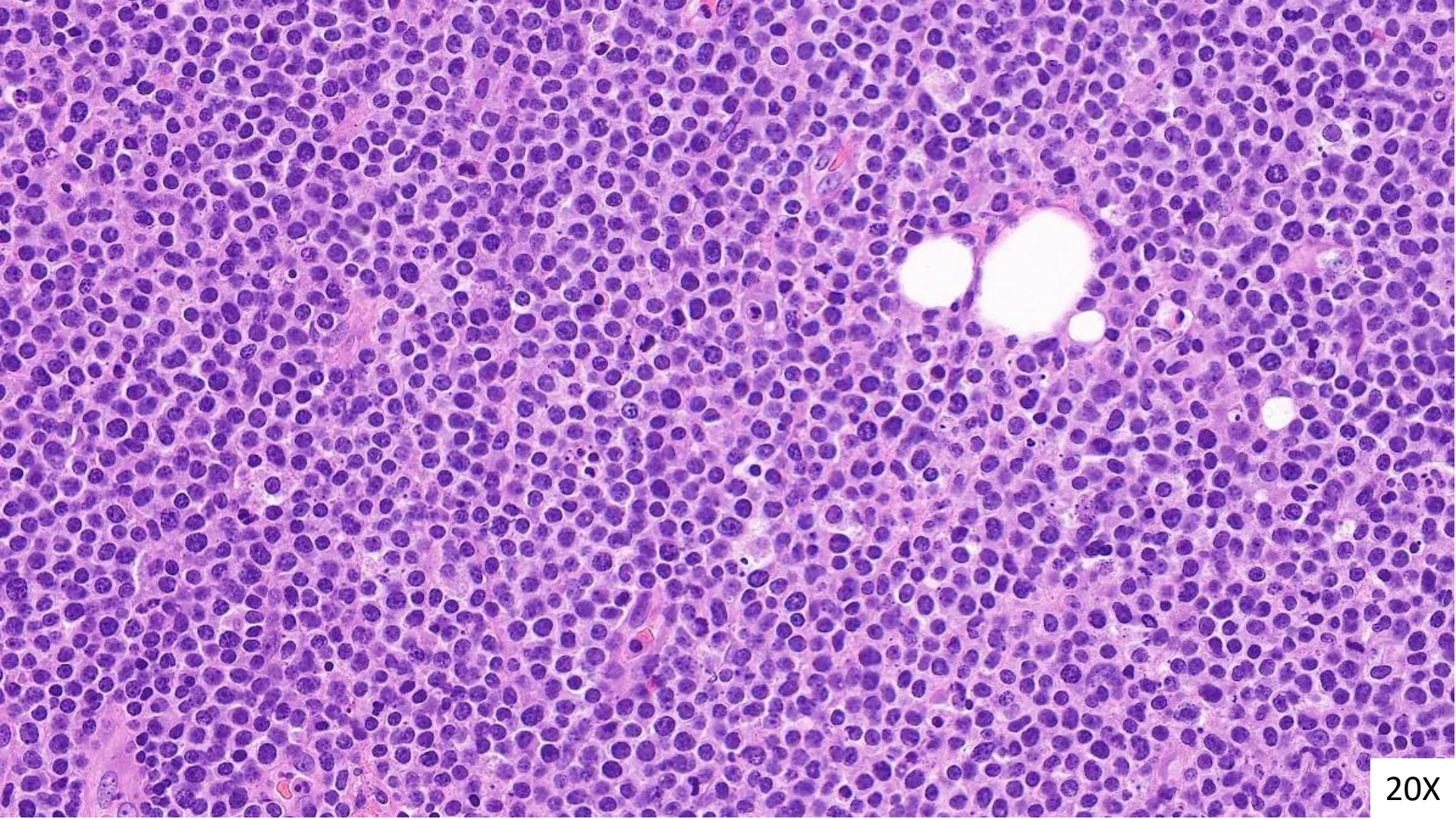
- Initial imaging findings concerning for obstruction.

Gross Description

- Two small intestine segments - significant serosal and lumen tumor with perforation.
- 17 x 11 x 8 cm in aggregate.
- Serosa thickened, largest lesion is 13 cm in greatest dimension.
- Invades the intestinal wall, mesentery and mucosa.
- Cut surface of the lesion is fleshy, rubbery and glistening.



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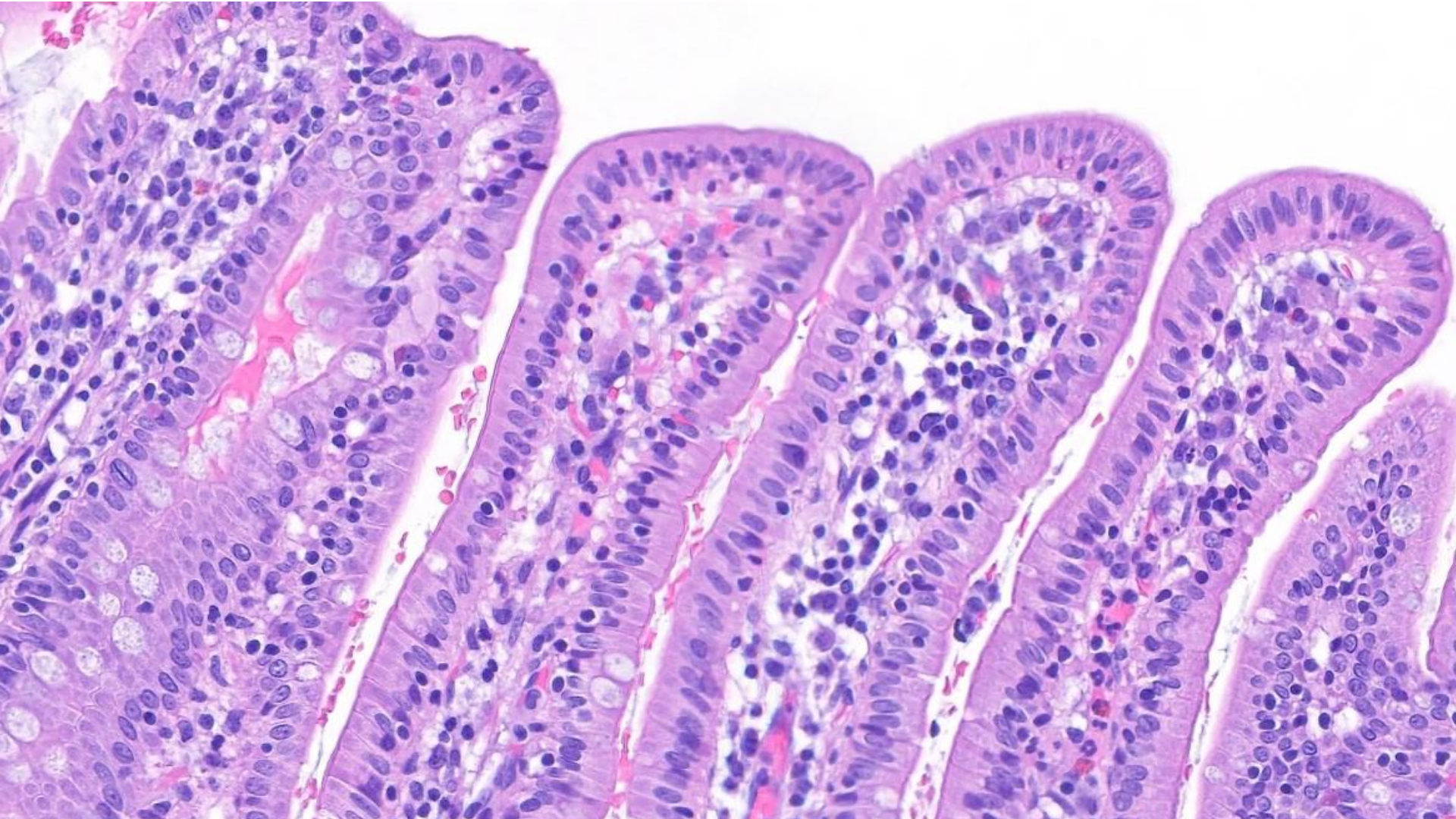

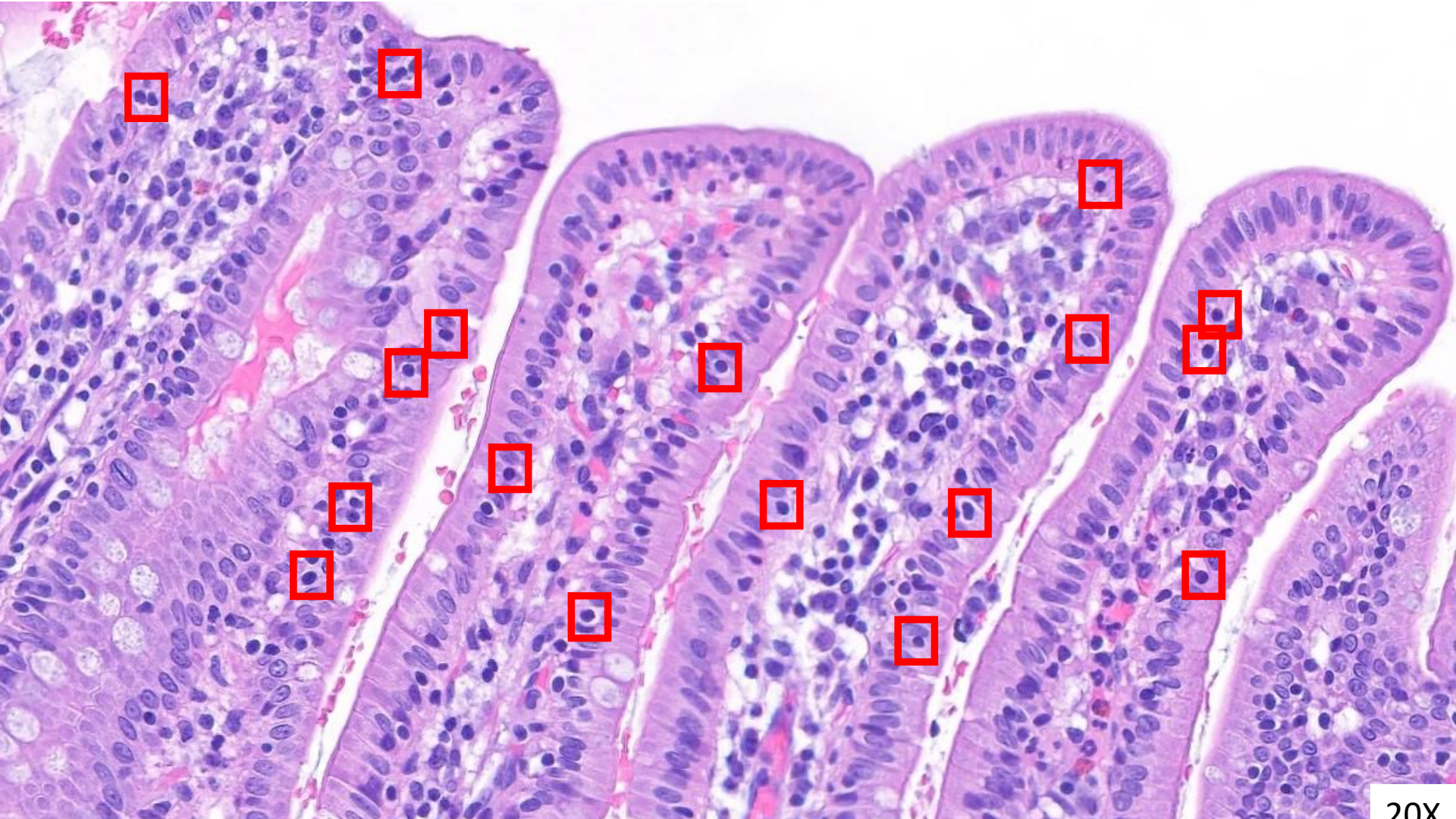
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Differential Diagnosis?

Morphologic Differential Diagnosis

Entity	Distinguishing Features
Extranodal marginal zone lymphoma	Small to medium with irregular, or "monocytoid" nuclei, inconspicuous nucleoli, and moderate pale cytoplasm

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Large B-cell lymphoma	Large B-cell morphology; no epitheliotropism

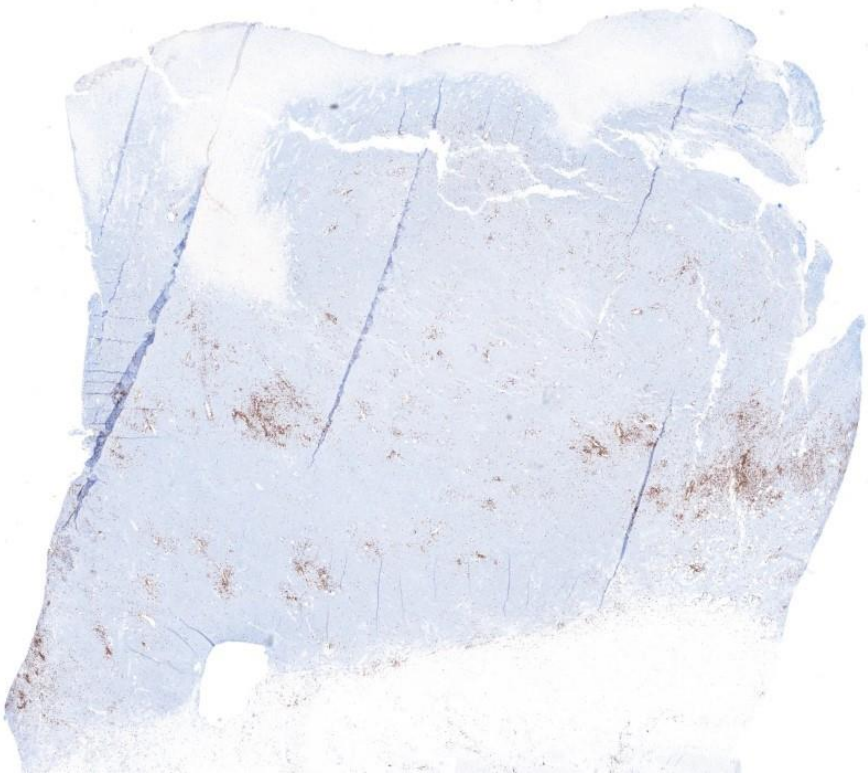
CD3

CD20

CD4

CD8

CD2 & CD5

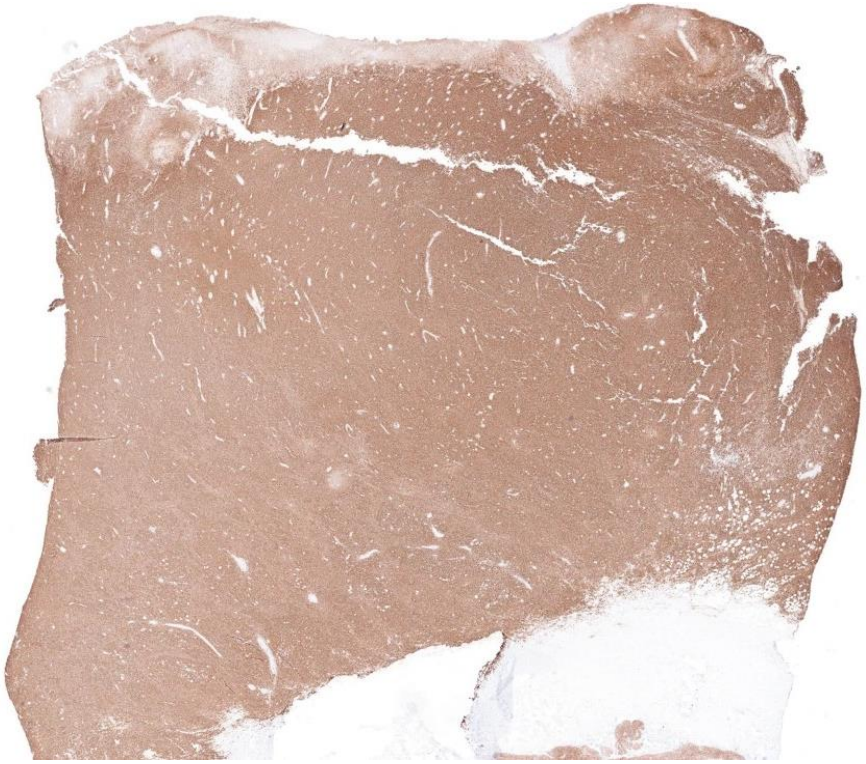


CD7

CD10

CD30

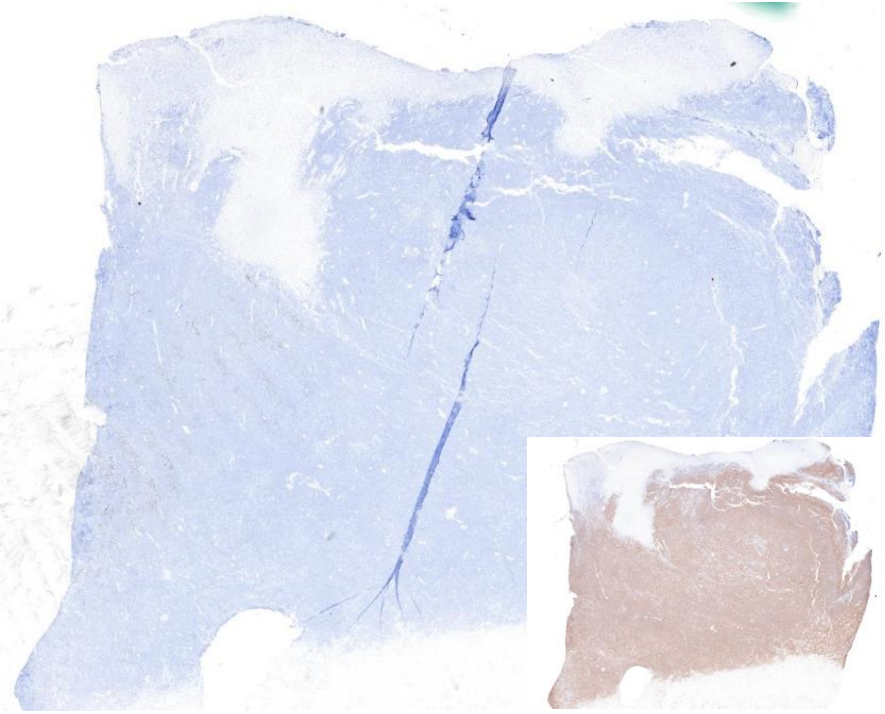
CD56

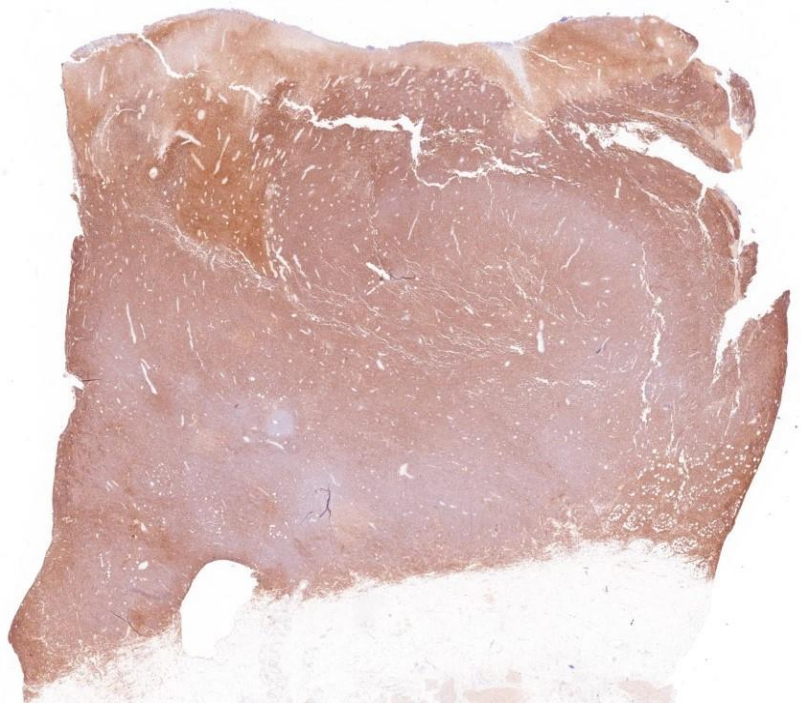


CD103

EBER

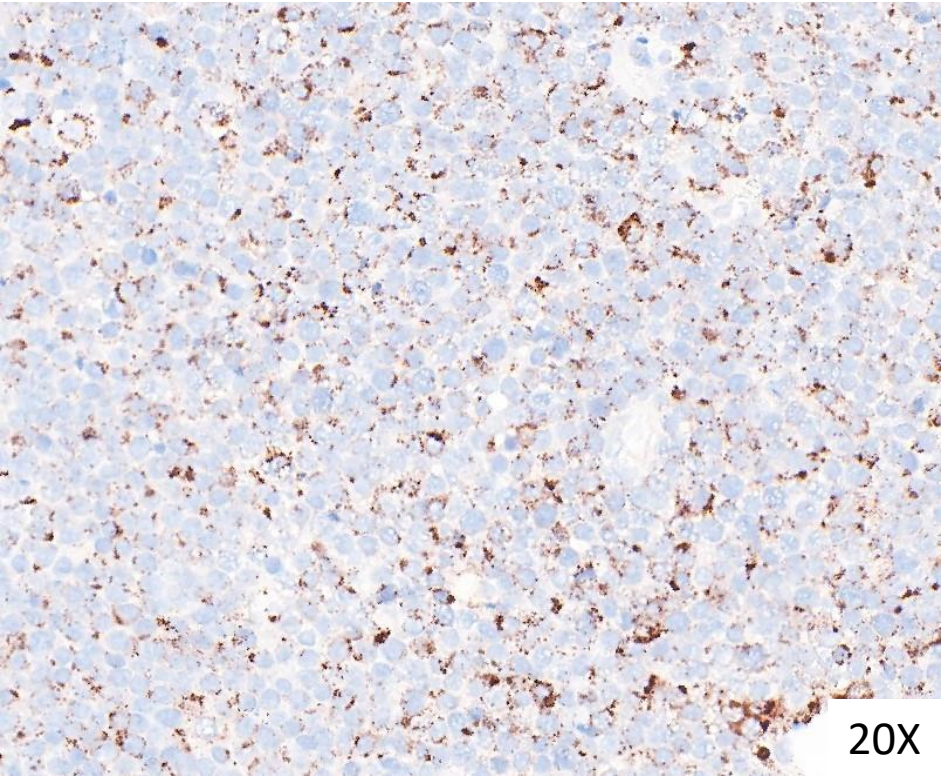
BF1



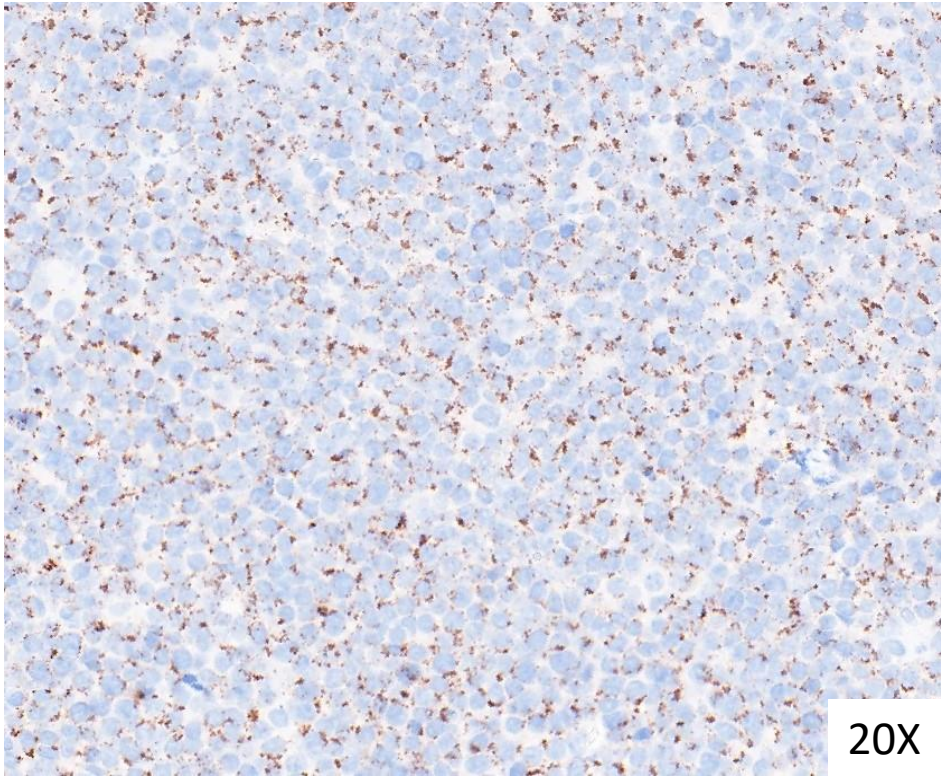


EBER+ RNA Control

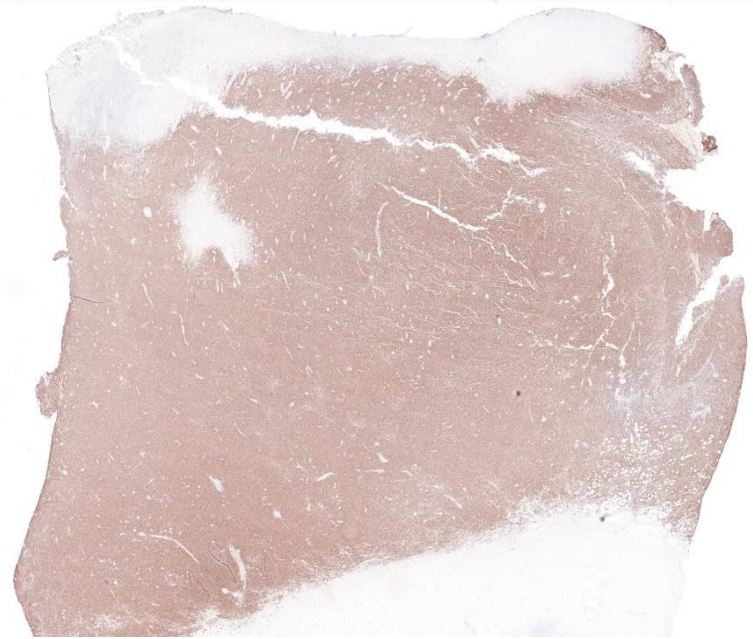
Granzyme B

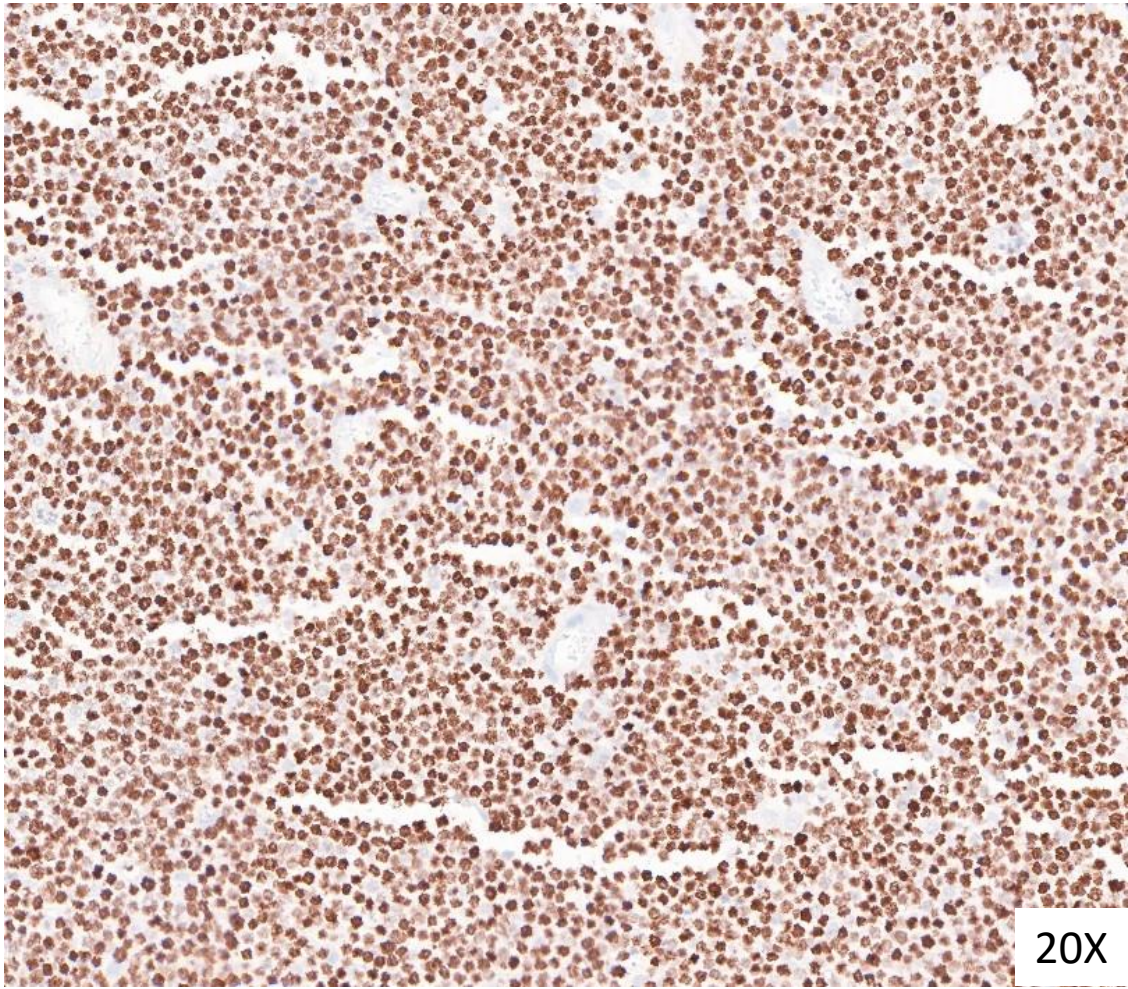


TIA1



Ki-67





Immunohistochemical Profile

+ (Positive)	– (Negative)
CD3	CD20
CD7	CD2
CD8	CD4
CD56	CD5
CD103	CD10
BF1	CD30
Granzyme B & TIA1	EBER
Ki-67 (>90%)	

Molecular studies

T cell clonality studies by PCR = POSITIVE

A clonal rearrangement is detected in T-cell receptor beta (TCRB) and gamma (TCRG) chain loci

T cell lymphoma studies by NGS = POSITIVE

1) ***NOTCH1***: Chr9(GRCh37):g.139390732G>A; NM_017617.3(NOTCH1):c.7459C>T; p.Gln2487* (44%)

2) ***STAT5B***: Chr17(GRCh37):g.40359659T>A; NM_012448.3(STAT5B):c.1994A>T; p.Tyr665Phe (87%)

3) ***TP53***: Chr17(GRCh37):g.7578190T>C; NM_000546.4(TP53):c.659A>G; p.Tyr220Cys (87%)

Final Diagnosis

Monomorphic Epitheliotropic Intestinal T-cell Lymphoma (MEITL)

Overview & Classification

Definition

An aggressive intestinal T-cell lymphoma composed of monomorphic medium-to-large lymphoid cells with consistent epitheliotropism. Formerly known as Type II EATL (enteropathy-associated T-cell lymphoma). Renamed in WHO 2016 and maintained in WHO 5th Ed (2022) and ICC 2022.

Classification Systems Compared

Classification	Terminology	Key Features
WHO 4th Ed (2008)	EATL Type II	Recognized as subtype; monomorphic cells, no celiac assoc.
WHO Revised 4th Ed (2016)	MEITL	Renamed; separated from EATL; CD8+/CD56+ profile
WHO 5th Ed (2022) & 2022 ICC	MEITL	Maintained; genetic hallmarks (*SETD2*, *STAT5B,* JAK-STAT pathway)

Presentation and Epidemiology

Epidemiology

Rare entity; ~20% of intestinal T-cell lymphomas in Western countries, higher in Asian populations.

No clear celiac disease association (unlike EATL).

Slight male predominance.

Median age 50s–60s. More common in Asia (China, Japan, Korea) and Mexico.

Presentation

- Abdominal pain, diarrhea, weight loss
- Intestinal obstruction/perforation
- B symptoms (~50%)
- Multifocal small bowel involvement
- Jejunum/ileum most common site

Staging & Spread

- Lugano staging (modified Ann Arbor)
- Stage I/II: rare at presentation
- Stage IV (disseminated): common
- Liver, spleen, bone marrow involved
- Peritoneal spread frequent

. WHO 5th Ed 2022 | Bhatt et al. Am J Surg Pathol 2020

Histology and Gross Description

Gross Pathology

- Mucosal ulceration, plaque-like lesions
- Transmural wall thickening
- Often multiple discrete lesions
- Perforation at presentation in ~30%
- Mesenteric lymph node involvement

Histopathology

Cell Morphology	Monomorphic medium-to-large lymphoid cells; round-to-irregular nuclei with prominent nucleoli; pale/clear cytoplasm; high mitotic rate
Epitheliotropism	Classic feature: intraepithelial lymphocytosis
Mucosal Architecture	Villous blunting and crypt destruction; may mimic celiac disease; ulceration and transmural infiltration common
Background	Minimal inflammatory background (contrast with EATL); no eosinophils/histiocytes

Differential Diagnosis

Entity	Key Distinguishing Features	IHC / Molecular Clues
Extranodal marginal zone lymphoma	Small to medium with irregular, or "monocytoid" nuclei, inconspicuous nucleoli, and moderate pale cytoplasm.	CD20+, PAX5+, CD79a+, B-cell lineage, IgM, CD21

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NK/T large granular lymphocytic leukemia	Fairly indolent course; peripheral blood NK/T-cell increase; no mass lesion; not typically epitheliotropic	CD56+/CD3–; no clonal TCR by standard methods; NK phenotype (KIR markers)
Hepatosplenic T-cell lymphoma	Sinusoidal infiltration of liver/spleen/BM; no intestinal mass; isochromosome 7q	CD56+/CD3+/CD4–/CD8–; γδ TCR; i(7q); no STAT5B mutations

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Molecular Genetics - MEITL

JAK-STAT Pathway Mutations (most frequent)

STAT5B	Gain-of-function mutations (N642H hotspot); ~70–80% of cases; major oncogenic driver; aberrant JAK-STAT signaling
JAK1/JAK3	Activating mutations; ~10–20%; co-occur with STAT5B or occur independently
GNAI2	Activating mutations; ~10%; G-protein signaling
STAT3	Less common; functional overlap with STAT5B

Epigenetic & Other Mutations

SETD2	Histone methyltransferase; loss-of-function ~25–30%
TET2	Epigenetic modifier; ~5–15%; aberrant DNA methylation
DNMT3A	Less common
TP53	Less common; associated with poor prognosis when present

Cytogenetic Abnormalities & Copy Number Alterations

Alteration	Frequency
9q31-34 gain	~50%
8q24 gain (MYC)	~20–30%
1q gain	~30%
8p23 loss	~25%

Roberti et al. Nat Commun 2016 | Küçük et al. Nat Genet 2015 | Nairismägi et al. Blood 2016 | ICC 2022

Prognosis & Survival Data

10–25%
5-Year OS
Overall population

7–10 mo
Median OS
All stages

~35–50%
CR Rate
With CHOP-based therapy

>70%
Relapse Rate
Within 1 year of CR

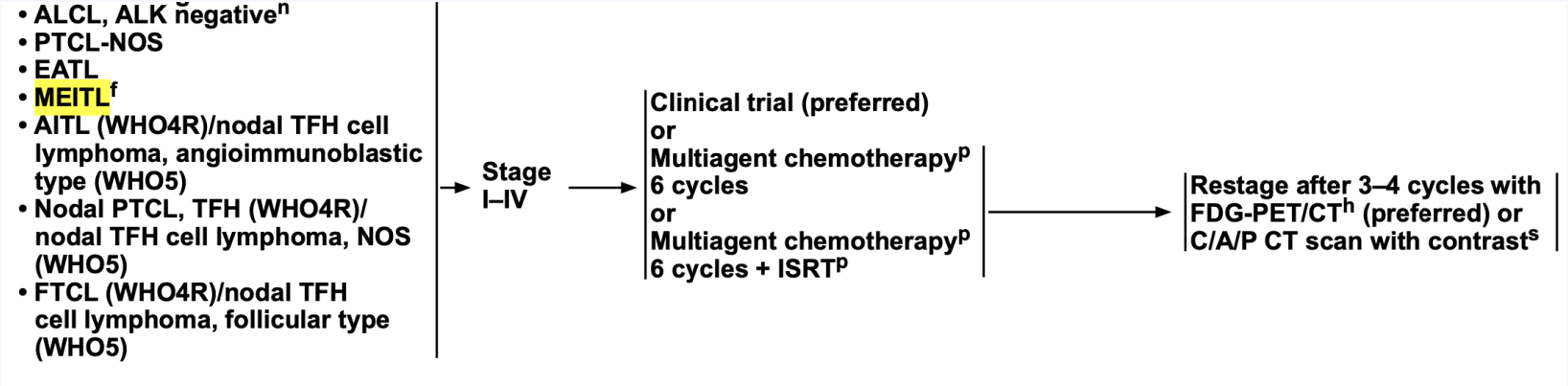
Key Studies with Survival Data

Study	N	Regimen	Outcome
Sieniawski et al. Blood 2010	31	CHOP ± ASCT	5-yr OS: 20% (MEITL subgroup); worse than EATL
Tse et al. Am J Surg Pathol 2011	31	CHOP-based	Median OS: 7 months; 1-yr OS: 39%
Tan et al. Leuk Lymphoma 2013	44	CHOP → ASCT	Median OS ~8.7 mo; ASCT in CR1 improved OS (15 vs 6 mo)
Delabie et al. Blood 2011	49	Various	5-yr OS: 11% for MEITL vs 39% for EATL
Nijeboer et al. Am J Hematol 2015	38	CHOP + ASCT	ORR 44%; CR 32%; Median OS 4.5 mo (MEITL)
Li et al. Ann Oncol 2020 (Asia cohort)	129	GDP/CHOP-based	Median OS: 13 mo; Stage IV: 8 mo; *STAT5B* mut: worse OS
Nathwani et al. Ann Oncol 2012 (NHL meta)	Multi-study	Various	Intestinal T-NHLs: 5-yr OS <20%; MEITL worst subtype

Therapeutics: Current Standards & Strategies

Frontline Therapy

- CHOP— standard but inadequate (~35% CR)
- CHOEP (+ etoposide) — preferred in fit patients <60 yrs; modest improvement in ORR
- Clinical trial



NCCN Guidelines T-cell Lymphoma 2023 | Sieniawski et al. Blood 2010 | Tan et al. Leuk Lymphoma 2013

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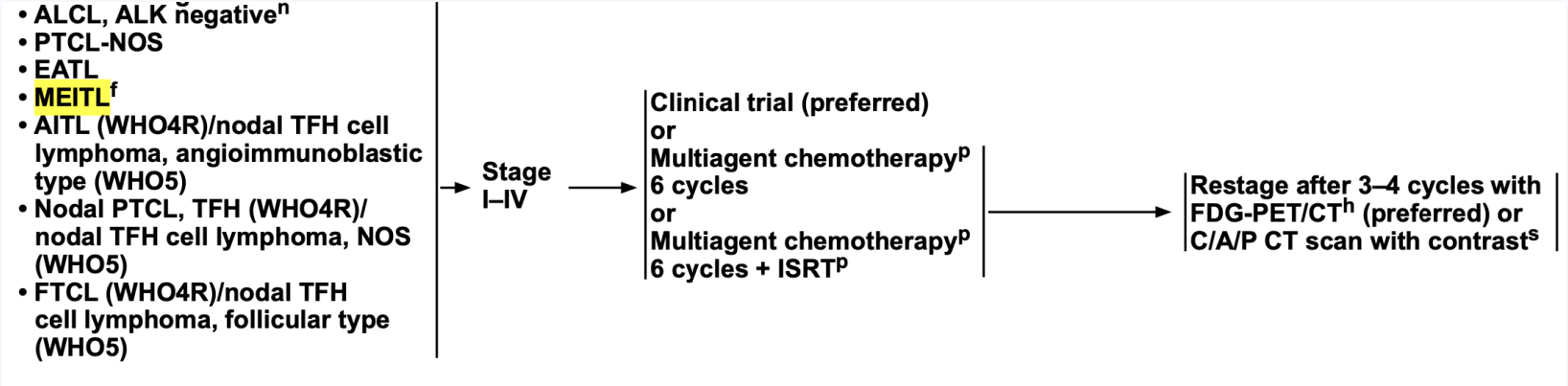

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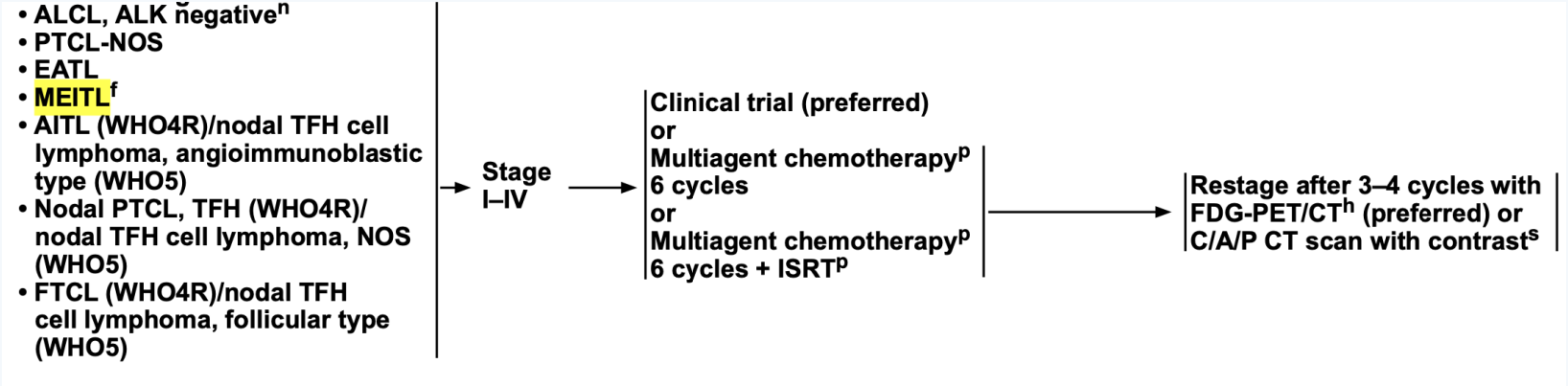
Relapsed / Refractory

- ICE, GDP, DHAP — salvage regimens; low response rates (ORR ~30%)
- Clinical trial enrollment strongly recommended
- Median survival at relapse: <3 months with standard salvage



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Emerging Therapeutic Targets

JAK Inhibitors

Rationale:

STAT5B N642H + JAK1/3 mutations → constitutive JAK-STAT signaling

Agents:

ruxolitinib, tofacitinib, itacitinib

Status: Preclinical / Case Reports

STAT5B Direct Inhibitors

Rationale:

STAT5B is the primary driver in ~80%; direct inhibition is rational target

Agents:

AK-2292 (investigational *STAT5* inhibitor); SH-4-54

Status: Preclinical

PD-1 / PD-L1 Checkpoint Blockade

Rationale:

PD-L1 expressed in subset; tumor immune evasion

Agents:

pembrolizumab, nivolumab

Status: Phase II (sporadic T-NHL trials)

Nairismägi et al. Blood 2016 | Lemonnier et al. Blood 2018 | Coiffier et al. JCO 2012 | Foss et al. JCO 2012

Key Takeaways

MEITL is a distinct, aggressive intestinal T-cell lymphoma, maintained as a separate entity in both WHO 5th Ed and ICC 2022.

IHC: CD8+/CD56+/CD103+/EBV– phenotype; cytotoxic T-cell immunophenotype with epitheliotropism.

STAT5B N642H is the dominant molecular driver (~80%).

Critical DDx: rule out EBV (NK/T nasal type), EATL (celiac, CD8–), and HSTL (sinusoidal, i7q). MEITL presentation can vary, not always mass forming lesion.

Dismal prognosis.

Emerging targets: *JAK* inhibitors, *STAT5B* inhibitors, checkpoint blockade (PD-1/PD-L1).

Thank you.

Questions / Comments ?

Cleveland Clinic