Case #1

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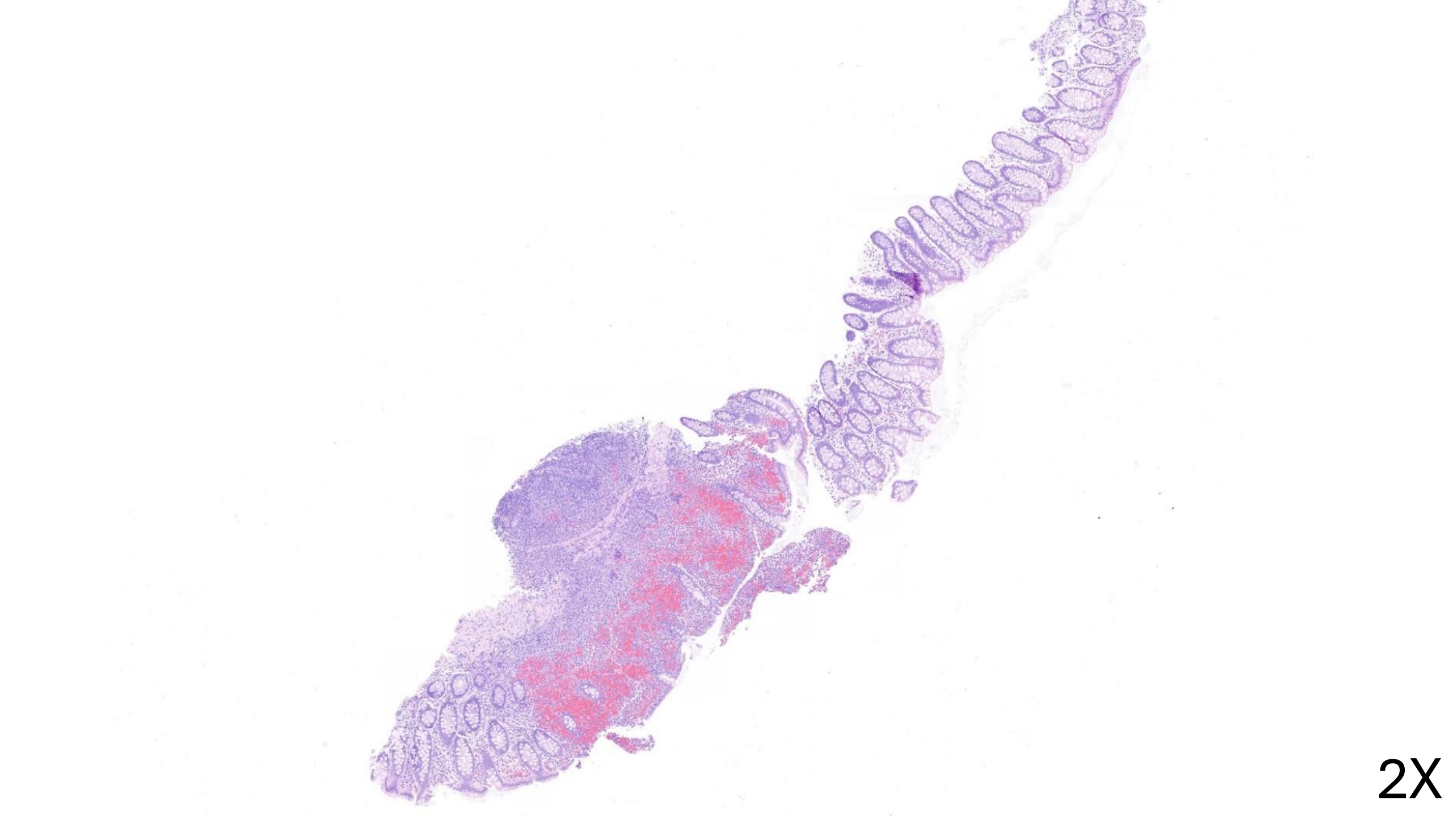
Hematopathology Fellow, PGY-5
5/27/2026

Cleveland Clinic

History

- 39-year-old female with history of constipation and rectal pain
- Colonoscopy identified:
  - 3 mm distal rectal polyp
  - 5 mm proximal rectal polyp
  - erythematous distal rectal mucosa.



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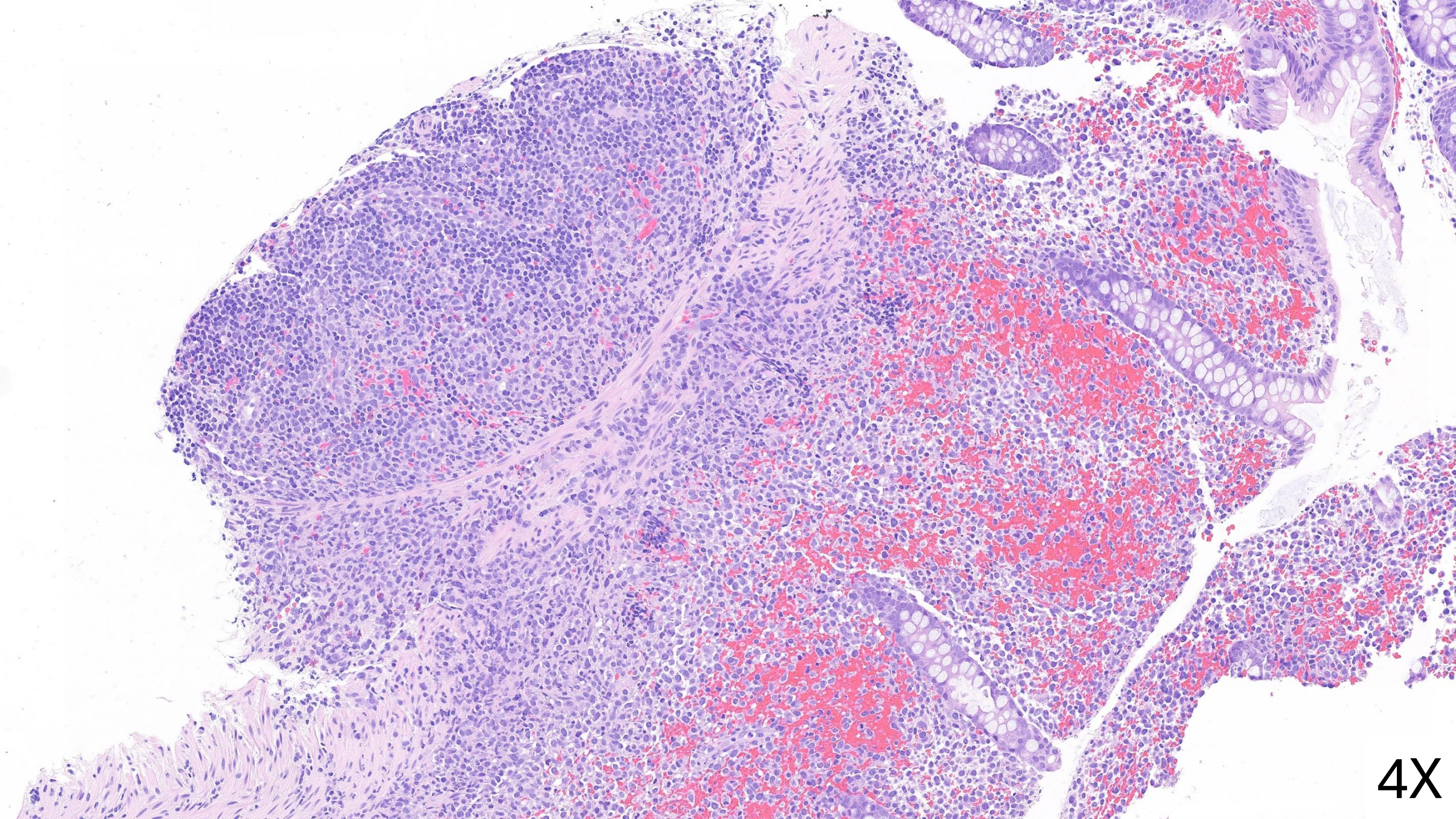
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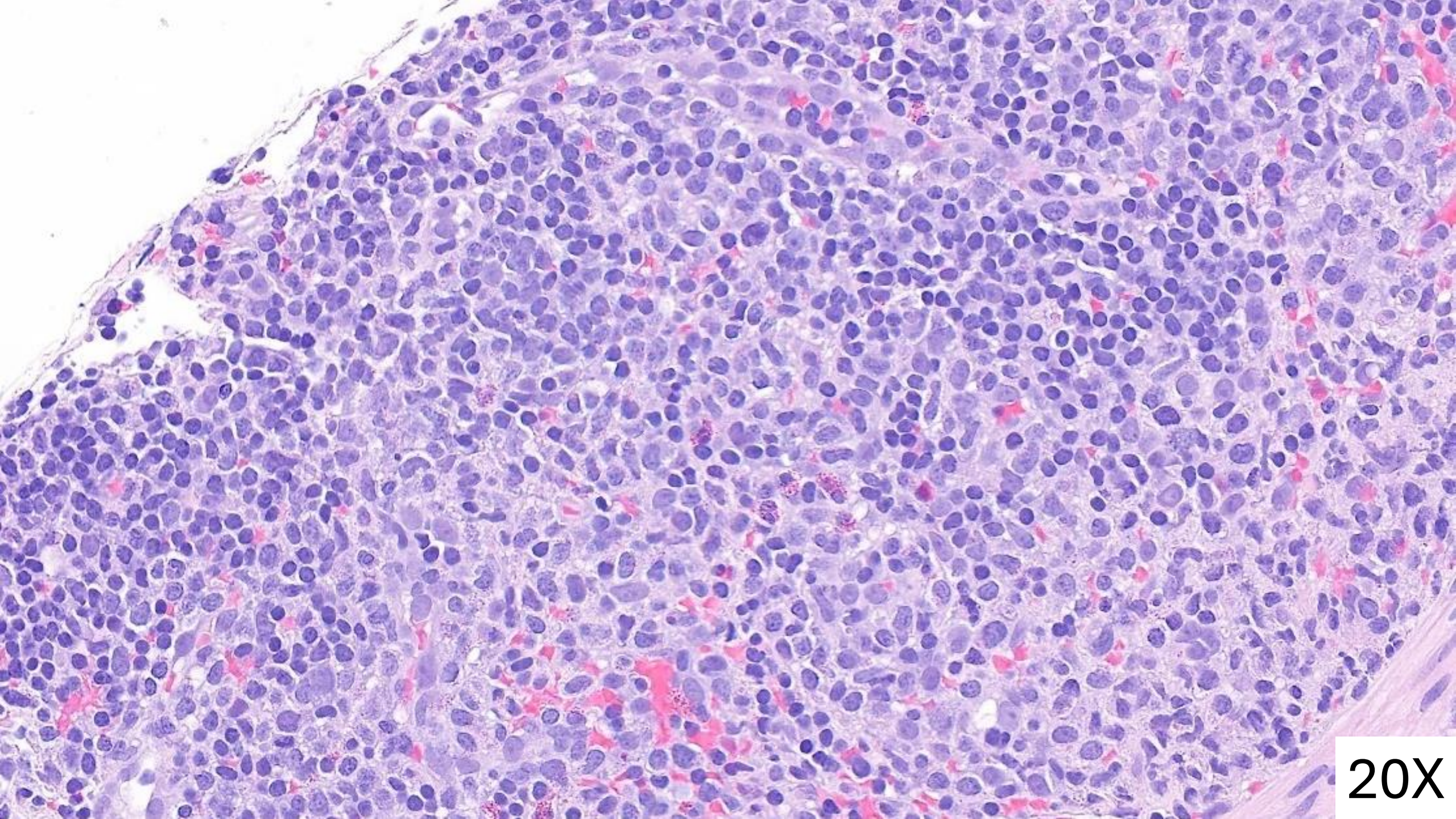
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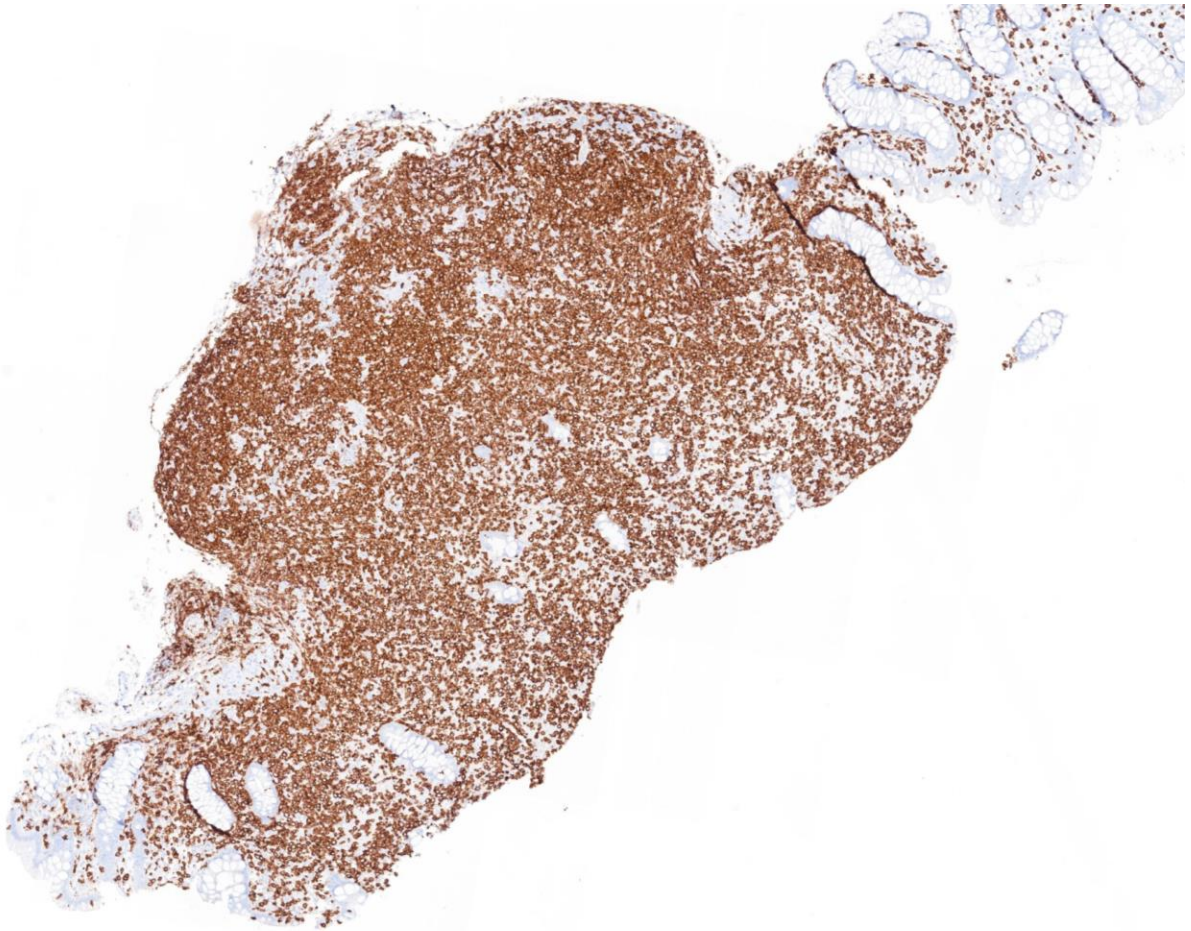
CD3



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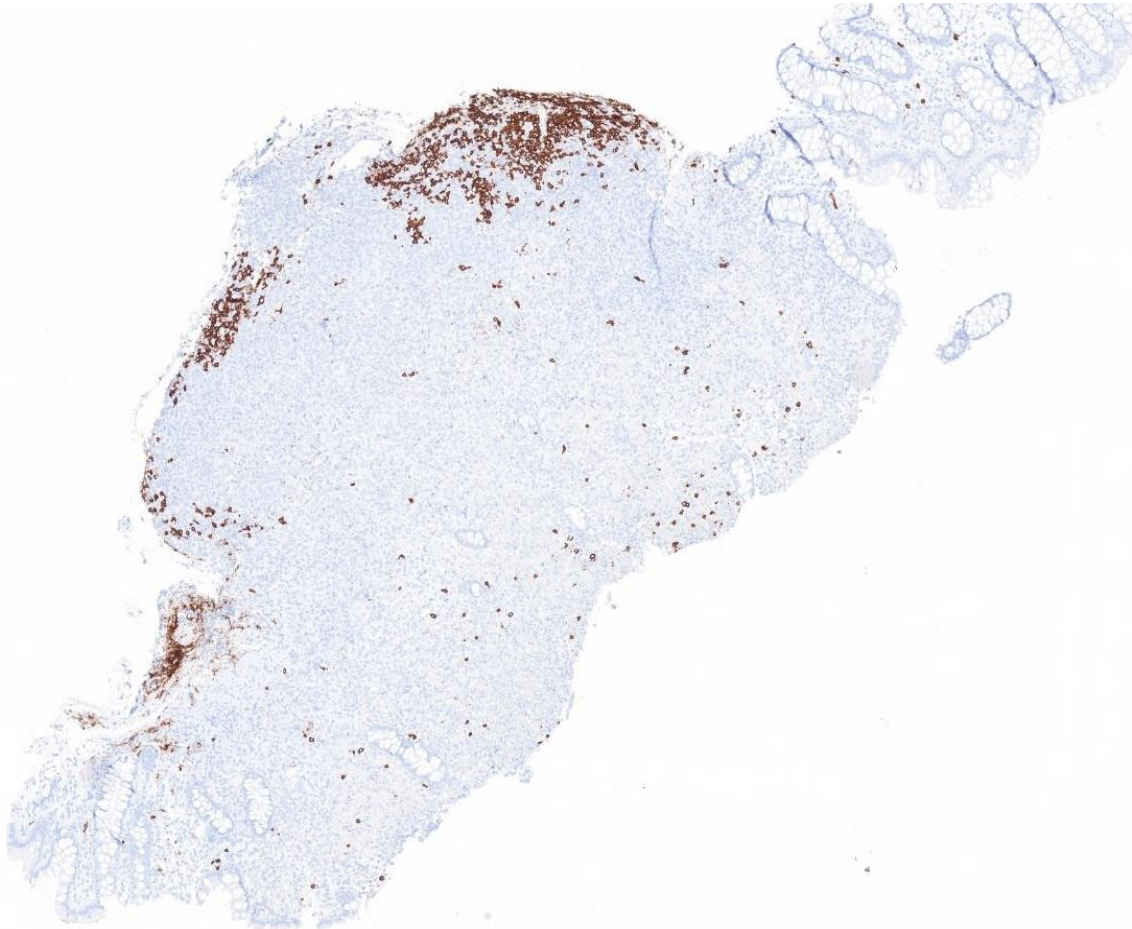
CD20



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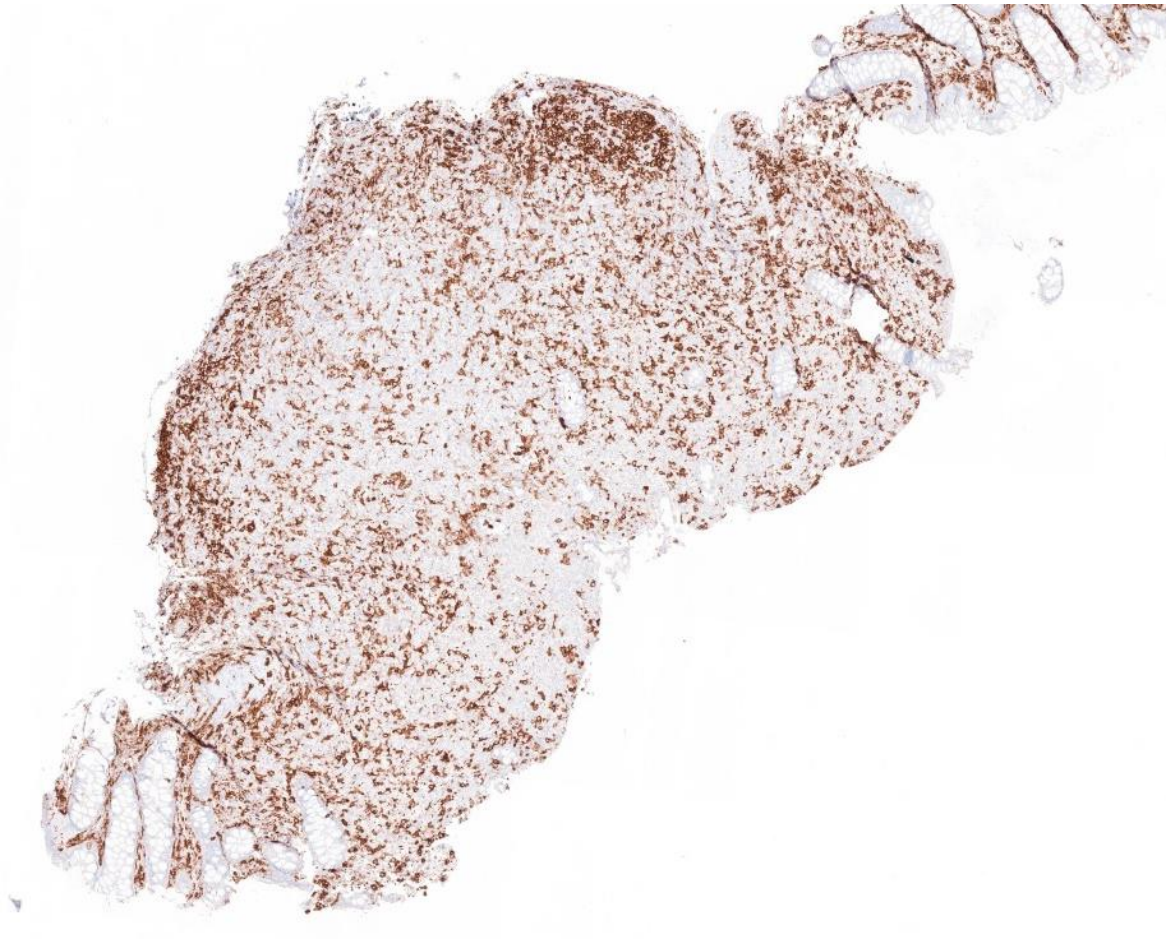
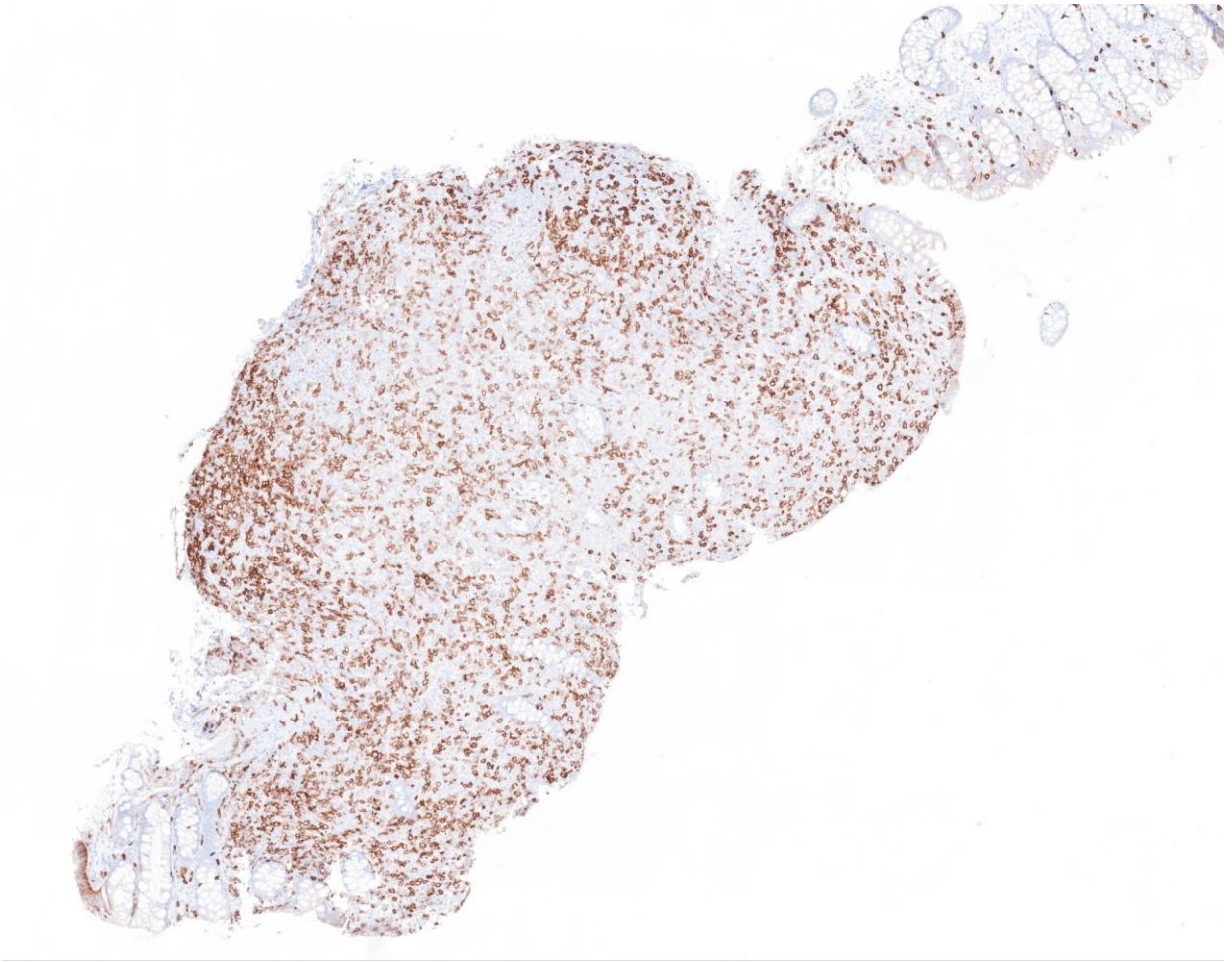
CD4



CD8



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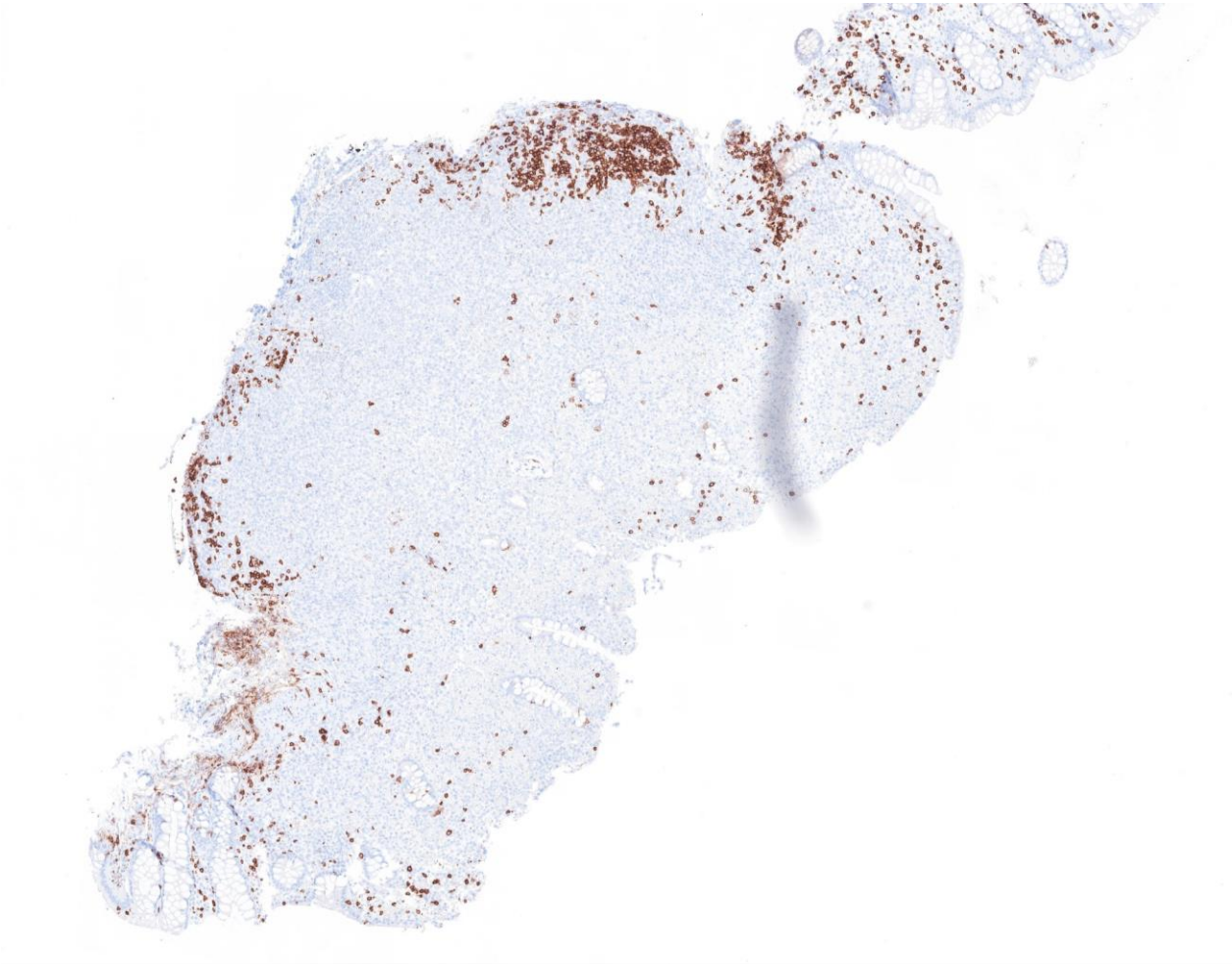
CD5



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CD7

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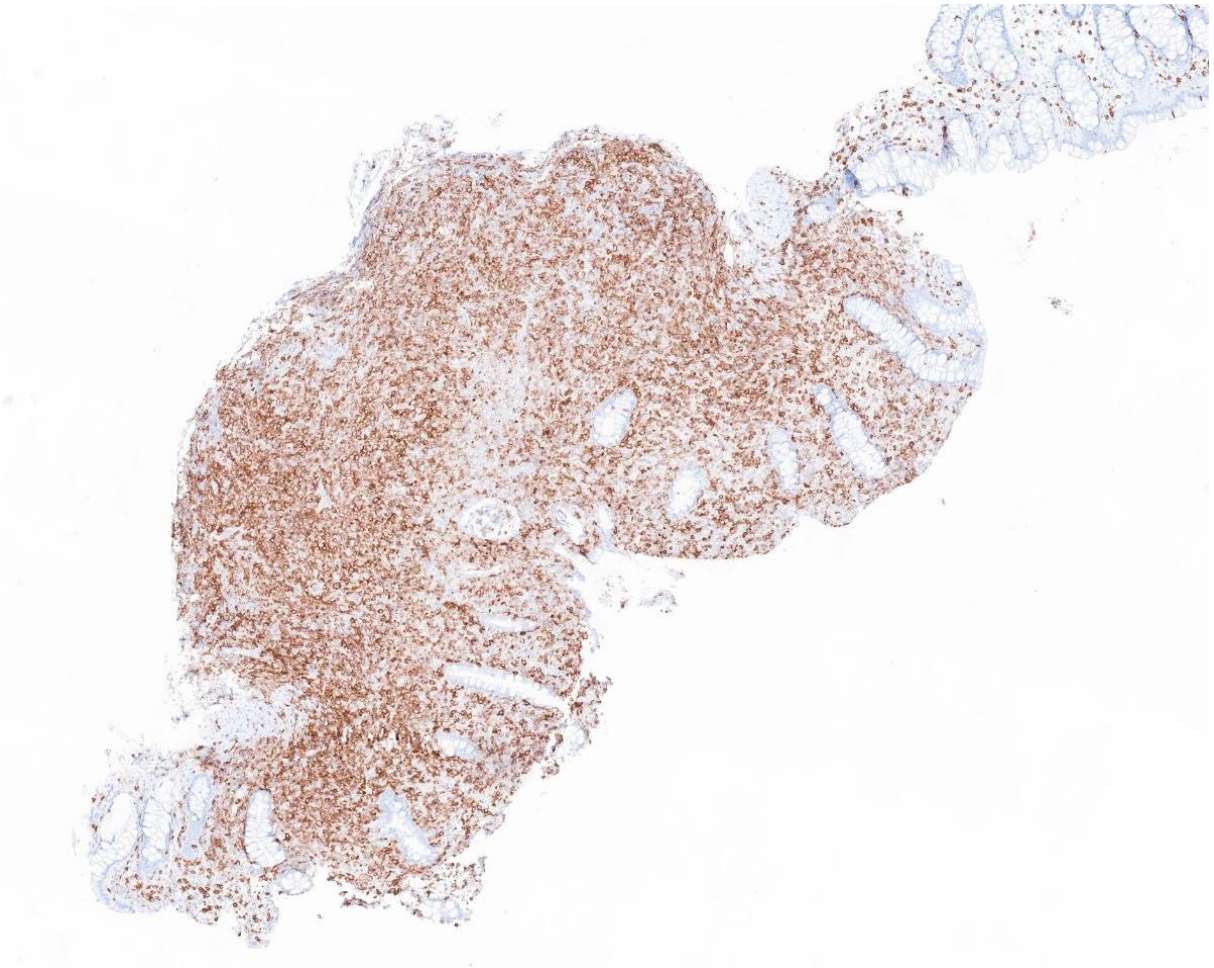
CD2



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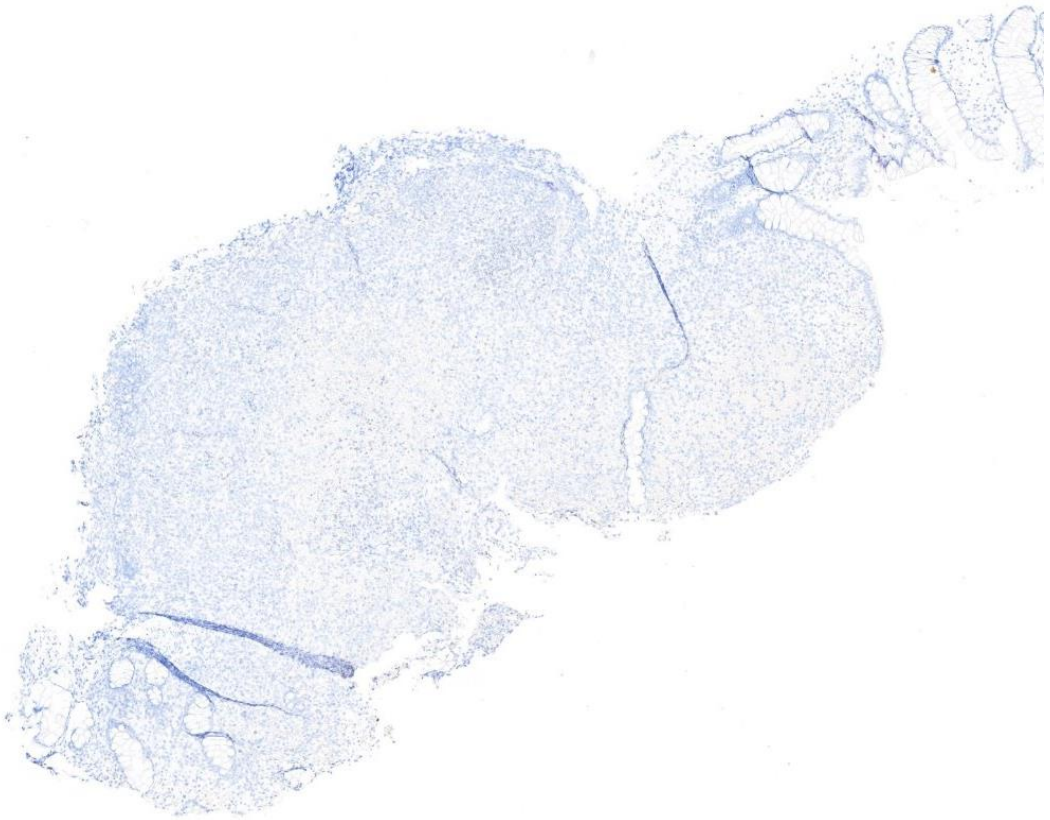
CD30 & ALK1



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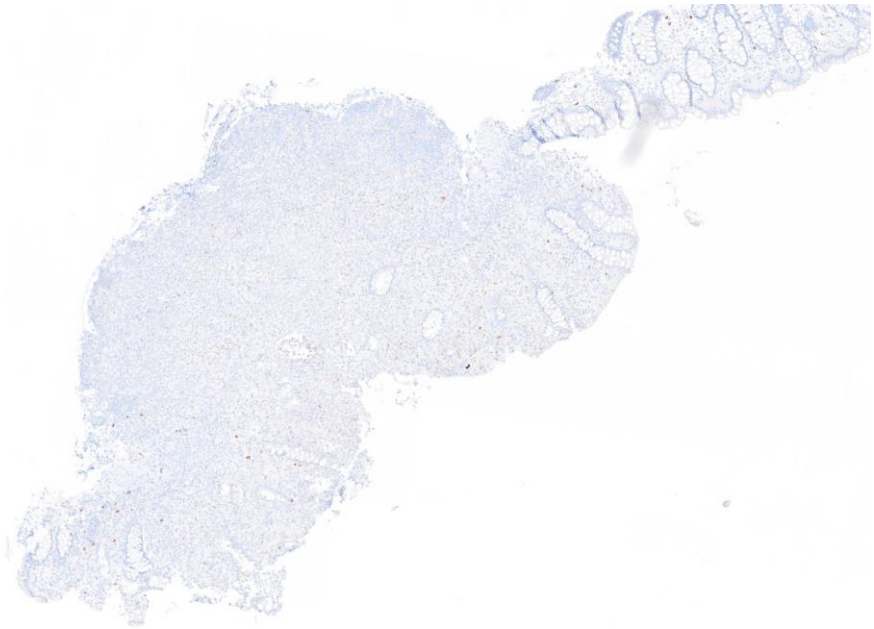
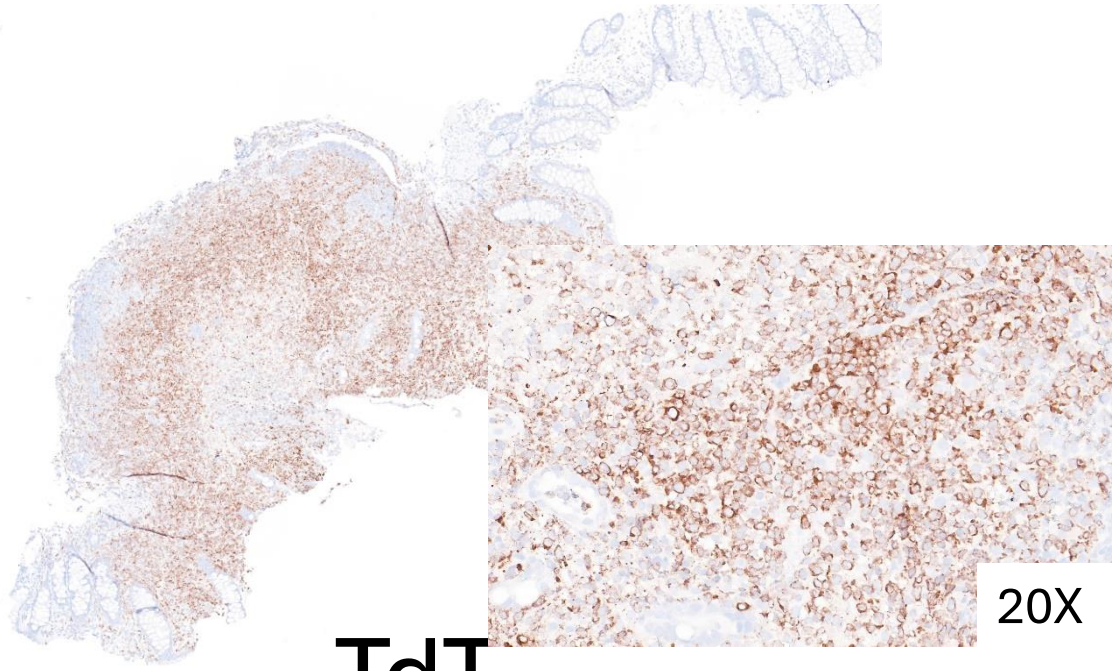
Granzyme B



Perforin



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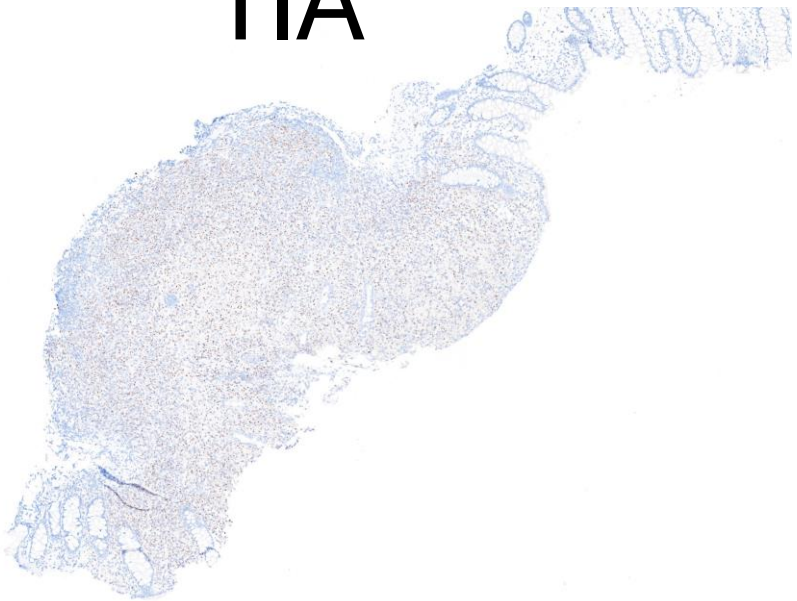
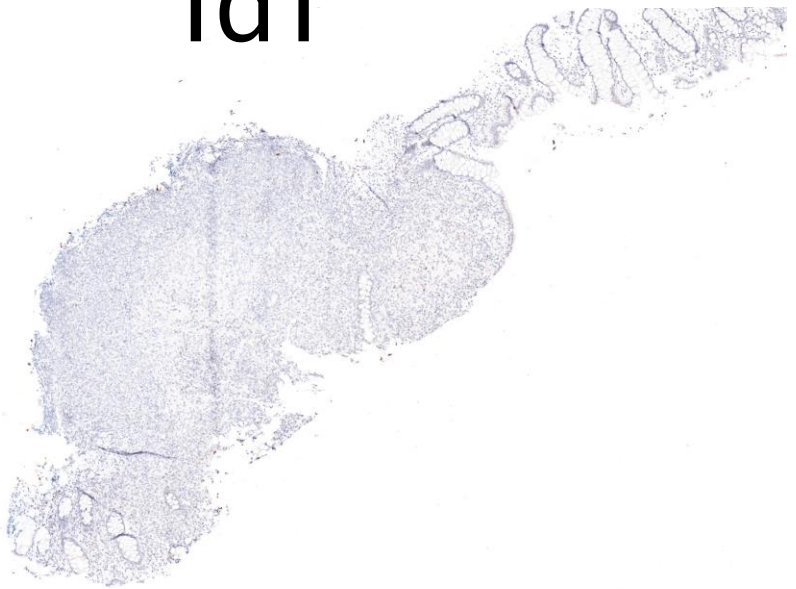
TIA



TdT



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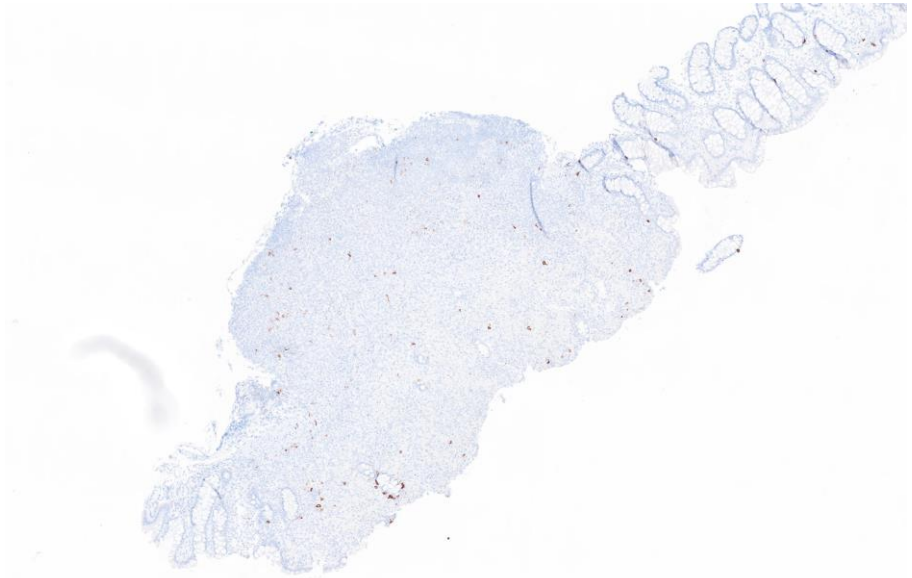
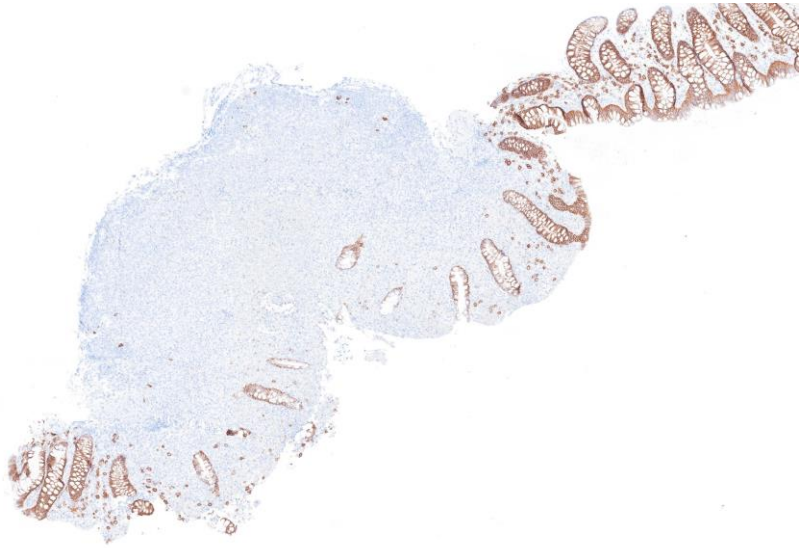
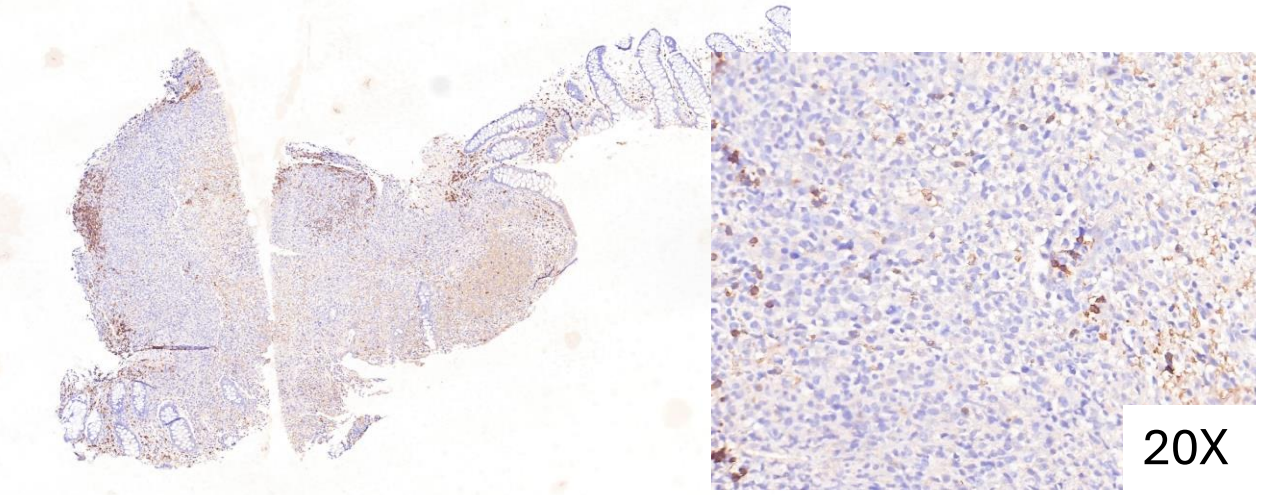
Langerin



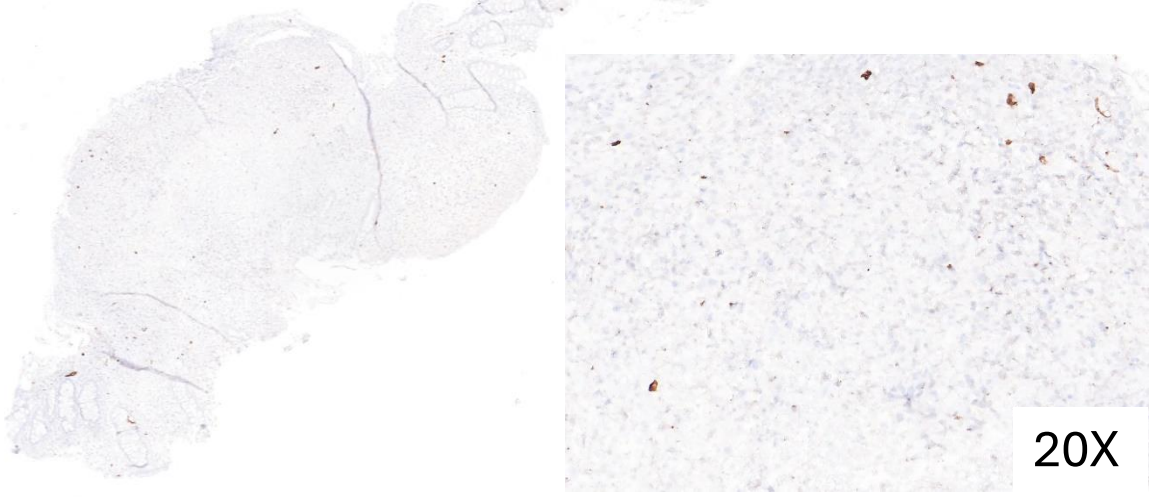
CD138



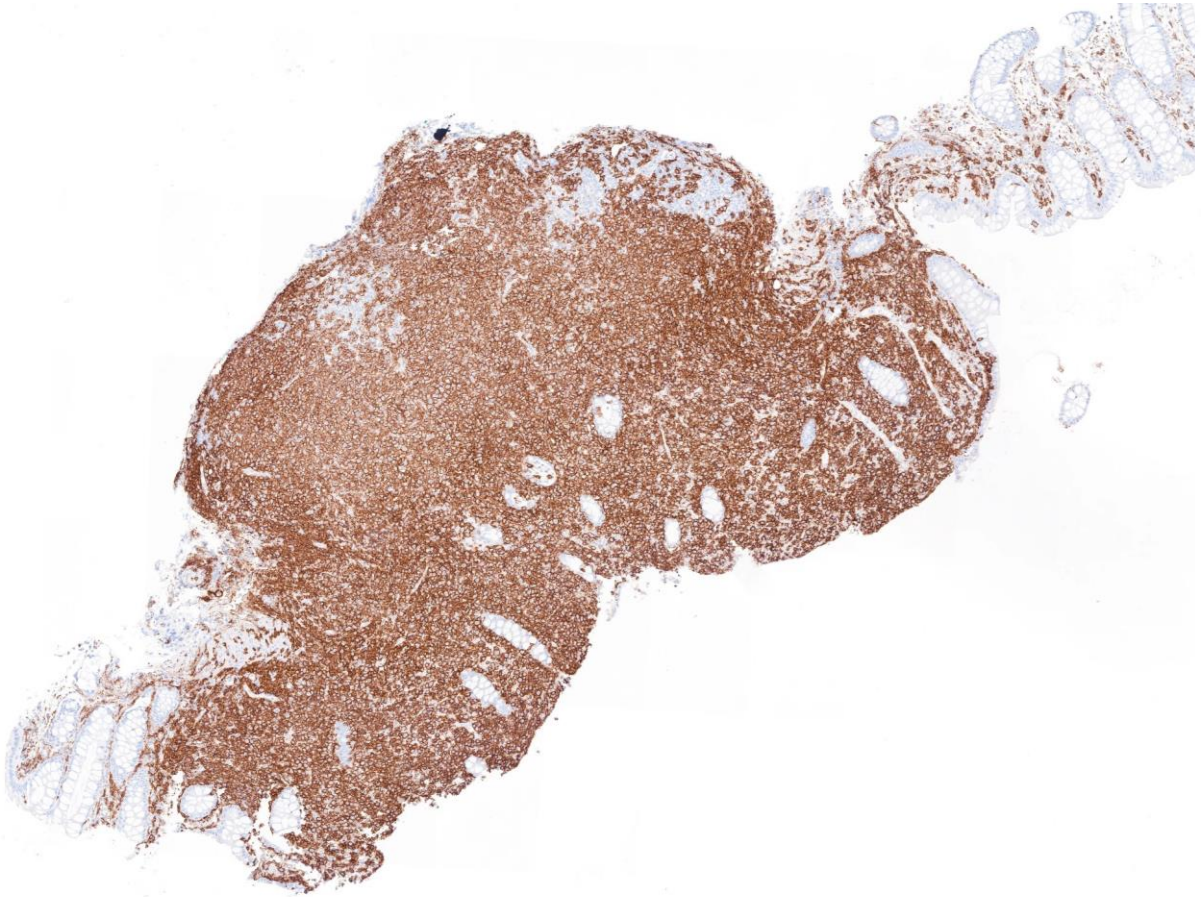
BF1



TCR delta



CD56



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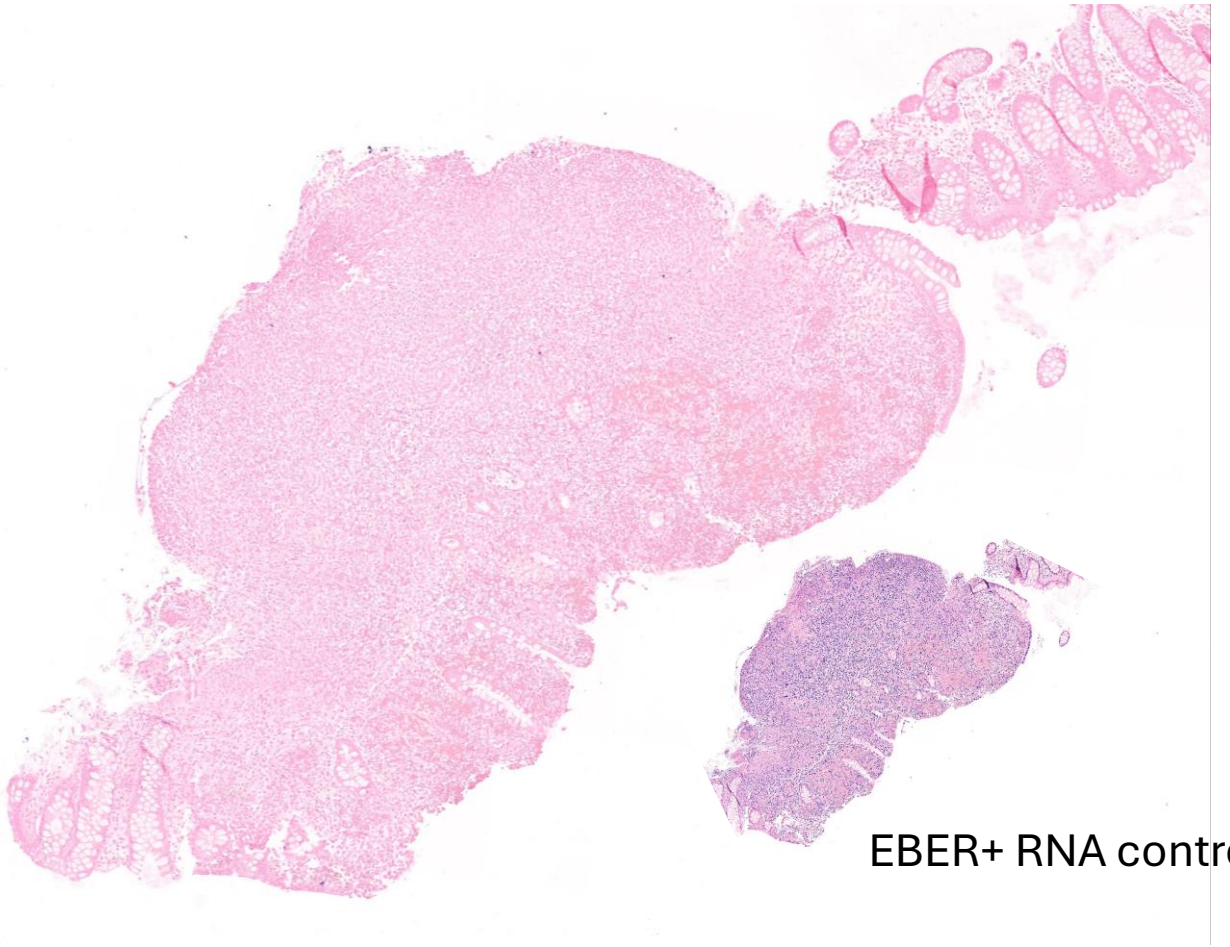
EBER



EBER+ RNA control

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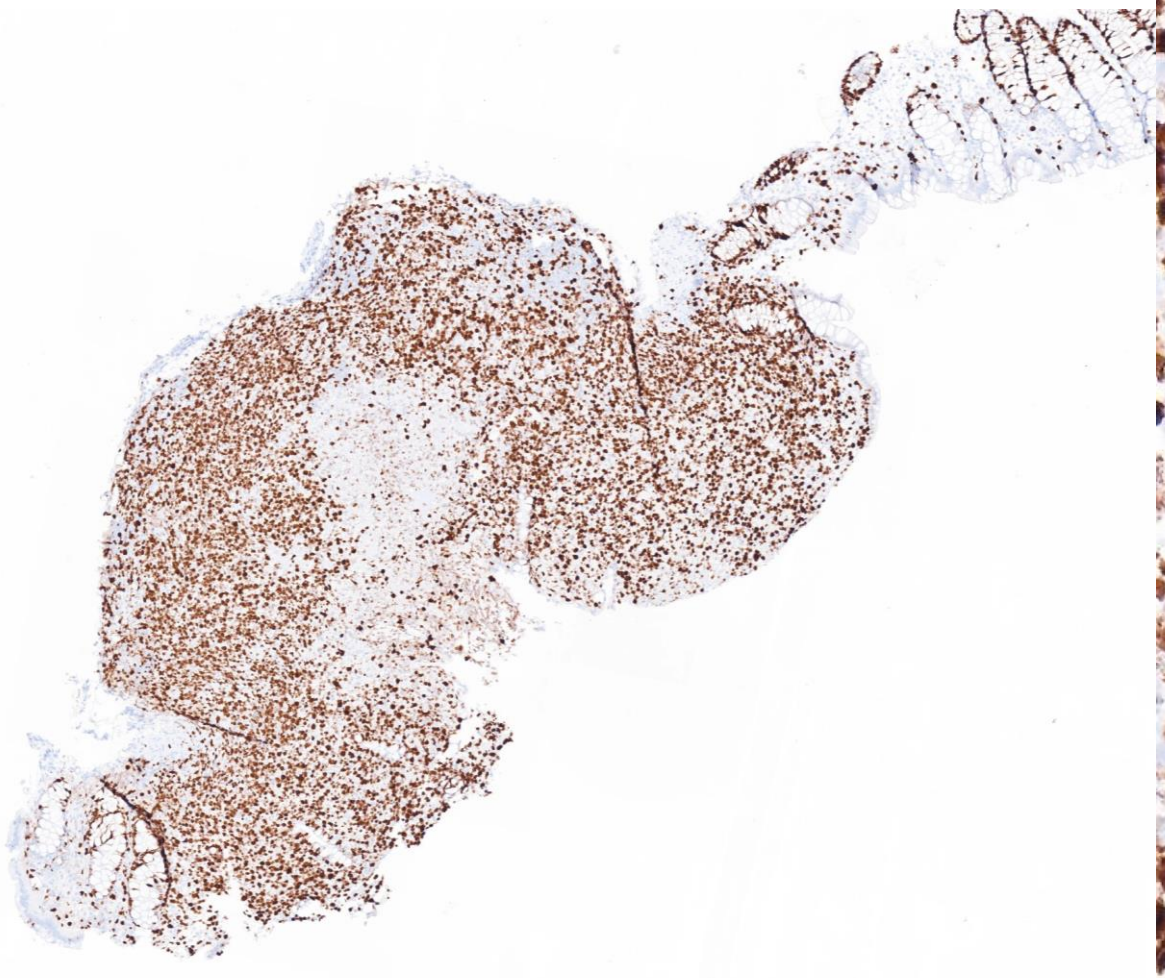
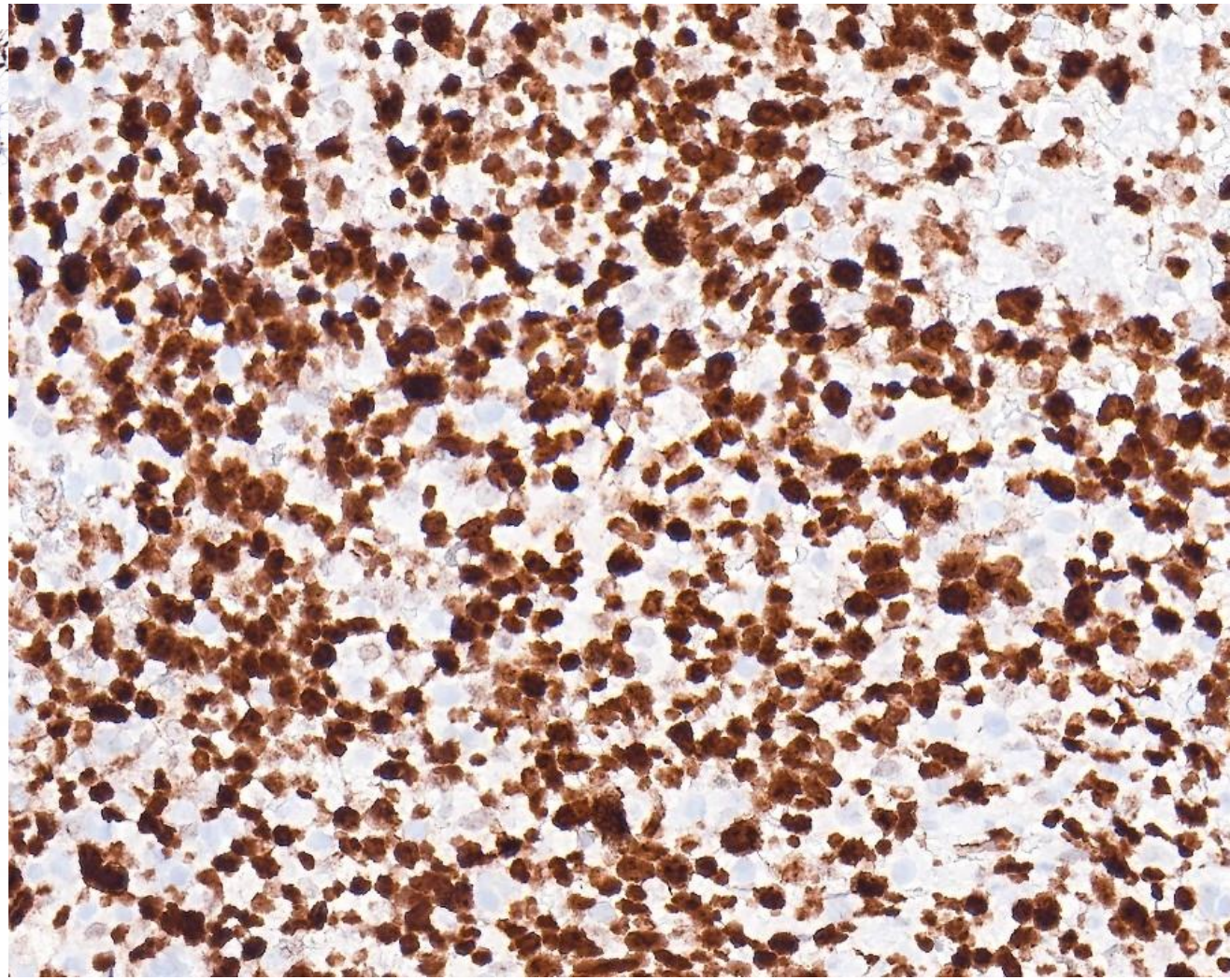
Ki67





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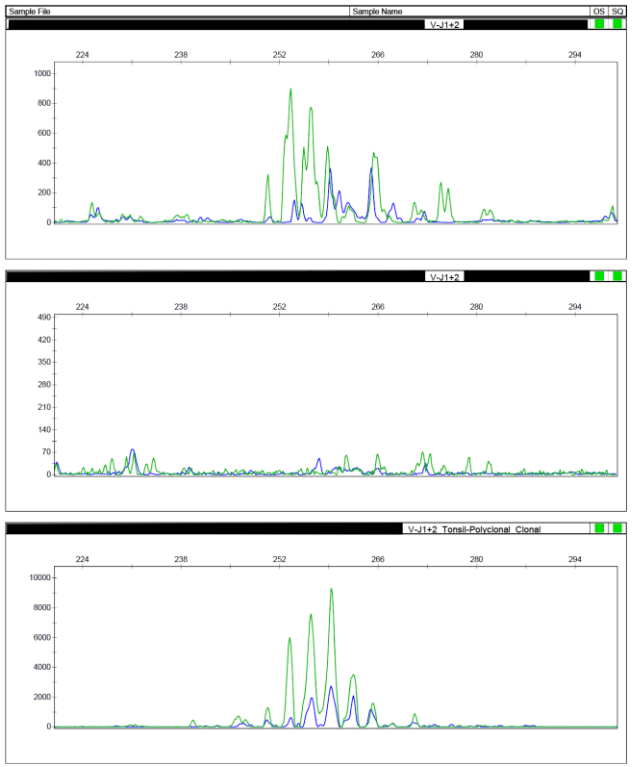
20X

IHC Summary

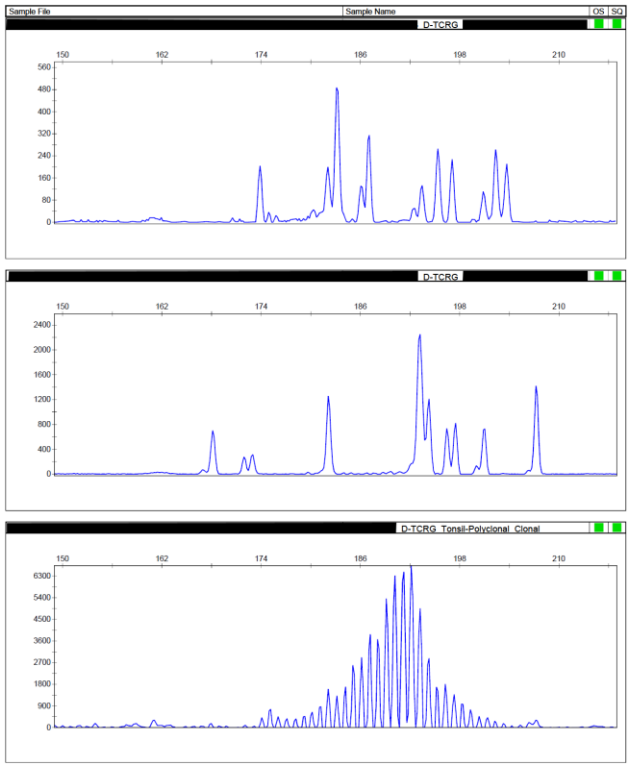
+ (Positive)	- (Negative)
CD2	CD4
CD3	CD5
CD7	CD8
CD56	CD30
Perforin	ALK1
Ki-67	TIA & Granzyme B
	BF1 & TCR Delta
	EBER
	Langerin
	CD138
	TdT

T-cell clonality PCR

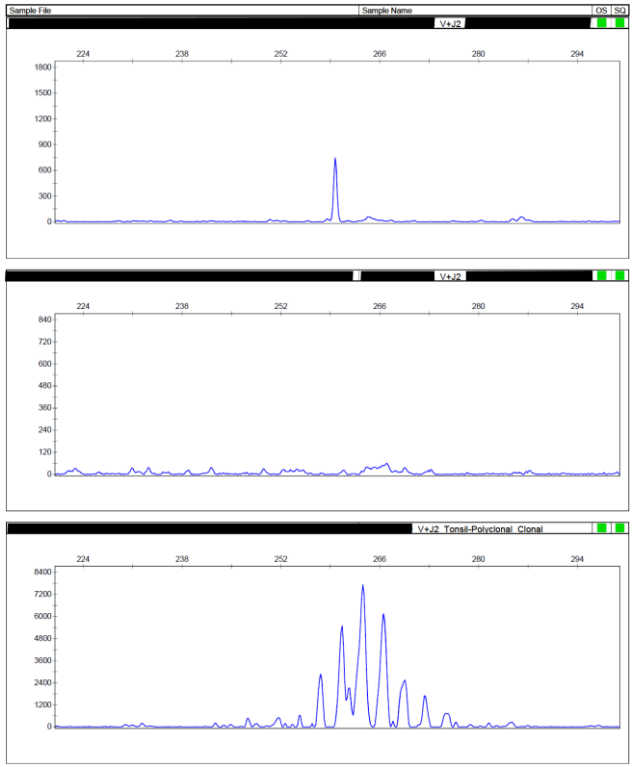
Interpretation: A clonal T cell receptor gene rearrangement is **NOT DETECTED**.



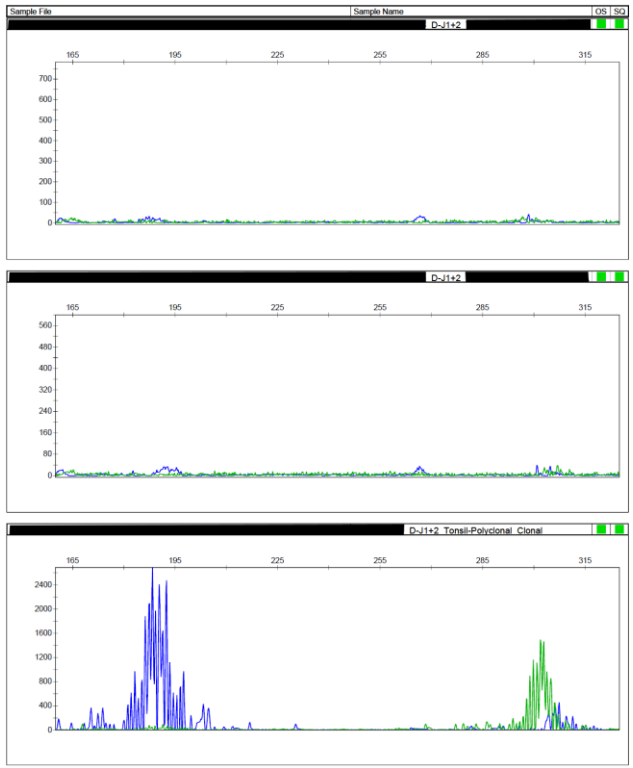
TCRB V-J1+2



TCRB V-J2



TCRB D-J1+2



TCRG

Final Diagnosis

Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract (iNK-LPD)

Clinical Features & Endoscopic Findings

Symptoms

- **Nonspecific abdominal pain** (most common)
- Nausea, vomiting, dyspepsia
- Diarrhea / altered bowel habits
- Often incidentally discovered

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GI Site Distribution

- **Stomach: most common site (~60%)**
- Small intestine (duodenum, ileum)
- Colorectum (less frequent)
- Multi-site involvement possible
- Upper GI > Lower GI in most series

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Systemic Features

- No peripheral blood involvement
- No lymphadenopathy or hepatosplenomegaly
- Normal lactate dehydrogenase (LDH)
- May show spontaneous resolution or persist despite therapy
- No reports of progression / transformation to a more aggressive lymphoma

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Endoscopic Appearances:

Flat or slightly elevated mucosal lesions • Superficial erosions or ulcerations • Polypoid protrusions • Reddened mucosa/erythema • Lesions may appear innocuous and mimic inflammatory conditions • Multiple or single lesions

NK cell vs. T cell

CLONALITY: NK cells lack immunoglobulin or TCR gene rearrangements. Clonality shown by **KIR immunophenotyping (restricted expression)**.

NK Cell	vs	T Cell

IMMUNOPHENOTYPE

NK Cell	T Cell
CD2+, CD3ε+ (cytoplasmic), sCD3−, CD56+, TIA-1+ **TCR−** (no rearrangement) KIR restricted expression → clonality marker	CD3+ (surface), CD5+/−, CD4+ or CD8+ **TCR+** *(αβ or γδ depending on subtype)* Loss of pan-T markers (CD7, CD5) common

MOLECULAR GENETICS / ANCILLARY TESTING

NK Cell	T Cell
iNK-LP-GI Limited data ***JAK3*** K563_C565del — recurrent somatic deletion ~30%	**iTCL-GI:** ***JAK/STAT*** ***TET2, KMT2D*** ***STAT3::JAK2***

Xiao W, et al. Recurrent somatic JAK3 mutations in NK-cell enteropathy. Blood. 2019. PMID: 31383643

Sharma A, et al. Recurrent *STAT3-JAK2* fusions in indolent T-cell lymphoproliferative disorder of the gastrointestinal tract. Blood. PMID: 29592893

Diagnostic Criteria & Challenges

Diagnostic Criteria (WHO 5th / ICC 2022)

- NK cell immunophenotype (CD3ε+, CD56+, surface CD3−)
- EBV negativity (EBER-ISH negative)
- Confined to GI mucosa — no systemic involvement

Key Diagnostic Challenges

Small biopsy samples: Often superficial; tissue may be insufficient for comprehensive IHC panel.

Ki-67: Proliferation index is variable, <50% in most cases, >50% in a subset of reported cases.

Overlap with reactive NK infiltrates: requires quantitative and qualitative assessment to exclude reactive hyperplasia.

Histologic mimicry: Cytological innocuousness mimics inflammatory bowel disease, celiac disease, or other inflammatory conditions.

Differential Diagnosis

Entity	Key Features	How to Distinguish
Extranodal NK/T-Cell Lymphoma, Nasal Type	Necrosis; angioinvasion; cytological atypia; systemic involvement; rapidly fatal	**EBV+ positivity; high-grade morphology; systemic staging positive**

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Aggressive NK-Cell Leukemia	Peripheral blood involvement; bone marrow infiltration; hepatosplenomegaly; systemic disease	**EBV+ positivity, CBC + differential; bone marrow biopsy; systemic staging**

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Normal GI NK-cell Infiltrate	NK cells physiologically present in GI mucosa	**Polyclonal KIR expression; no mass lesion; clinical context**

Thank you.

Questions / Comments ?