Monthly Multi-Institutional Hematopathology Interesting Case Conference

with **Fahad S. Ahmed, MD.**
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2/26/2025

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TEMPLE HEALTH

and **Bhaumik Shah, MD.**
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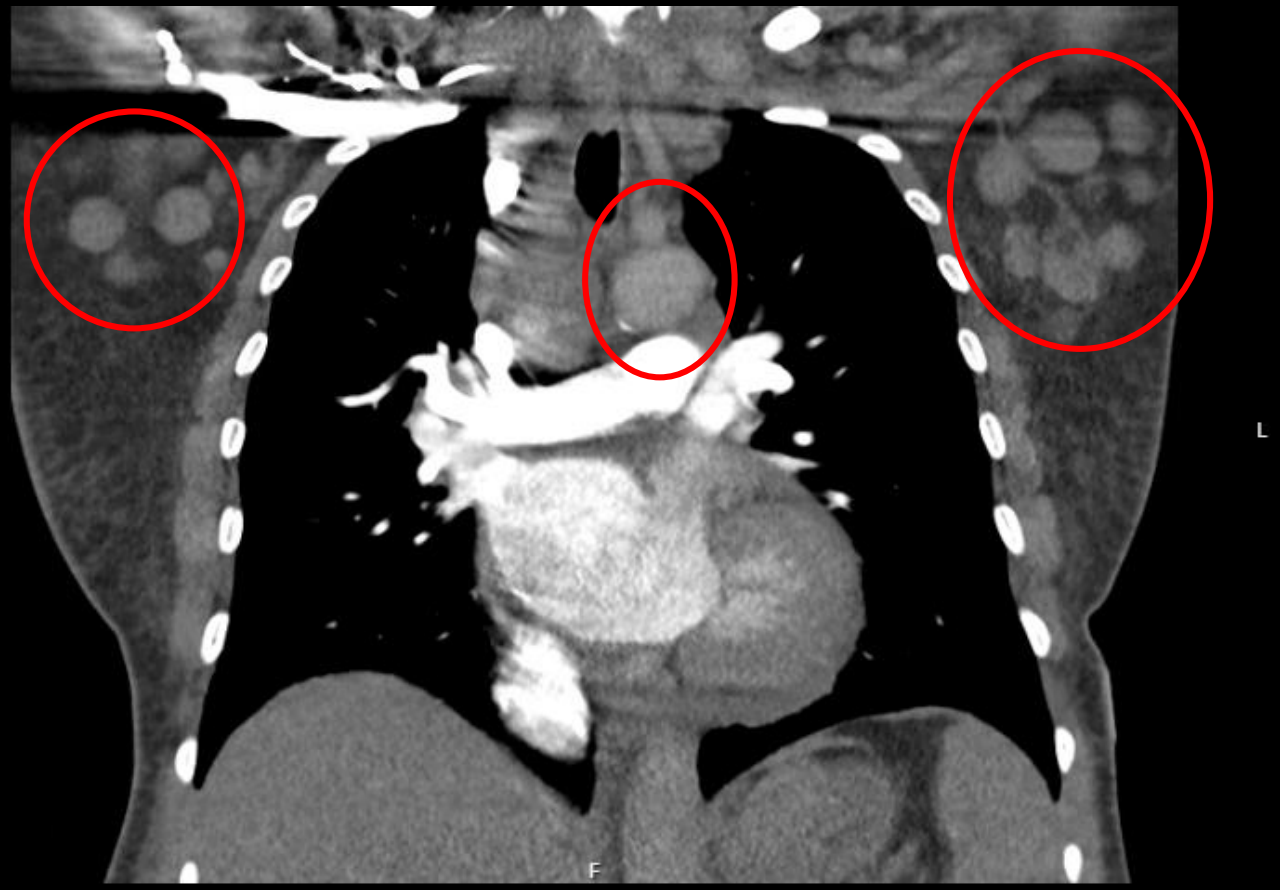
Case 1

- **63 years old Female**
- **Clinical:**
  - Fever, Fatigue and diffuse lymphadenopathy
  - CBC: Anemia with thrombocytopenia.
  - CTA: Bulky mediastinal and axillary lymphadenopathy
- **Procedure:**
  - **Axillary lymph node excisional biopsy**
- **Pathology:**
  - **Gross:** a 3.0 x 2.0 x 1.5 cm Lymph node



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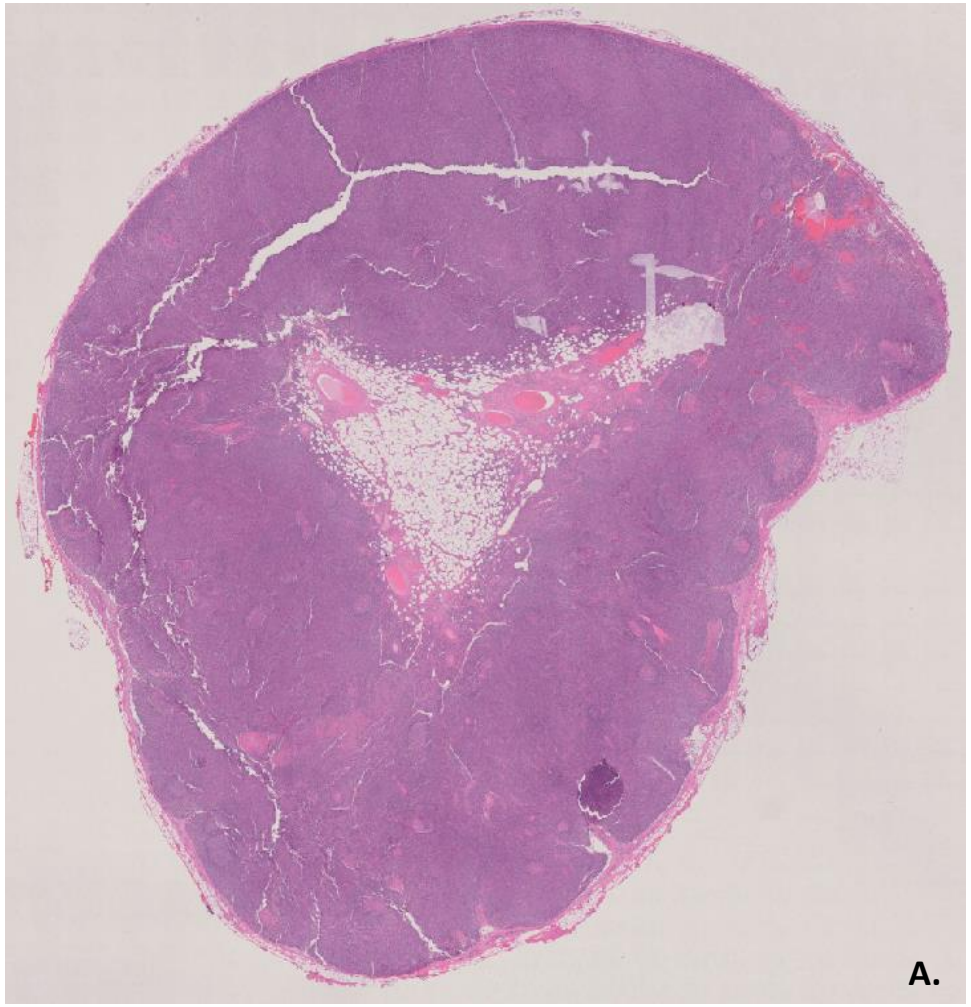

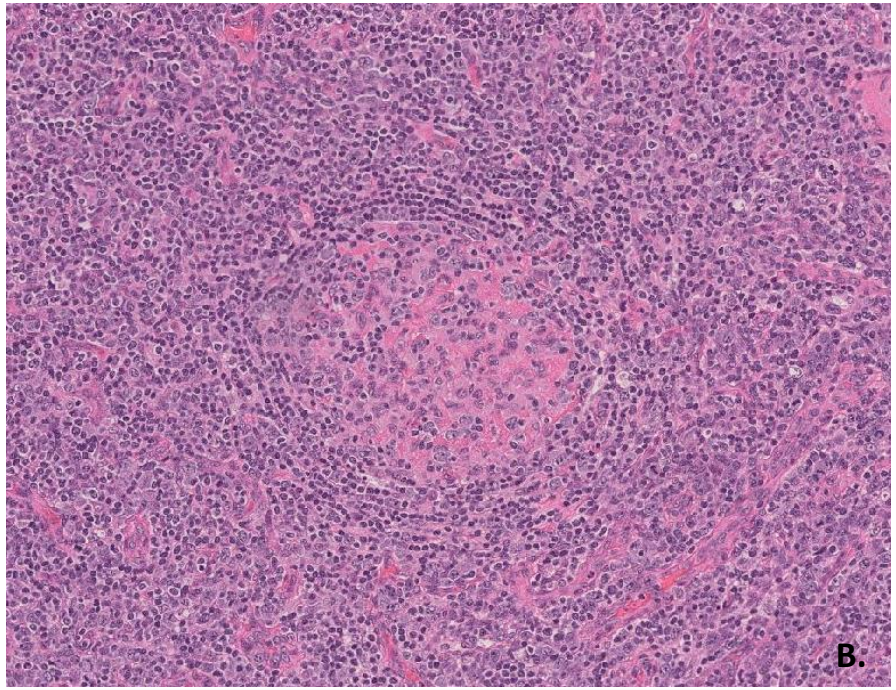

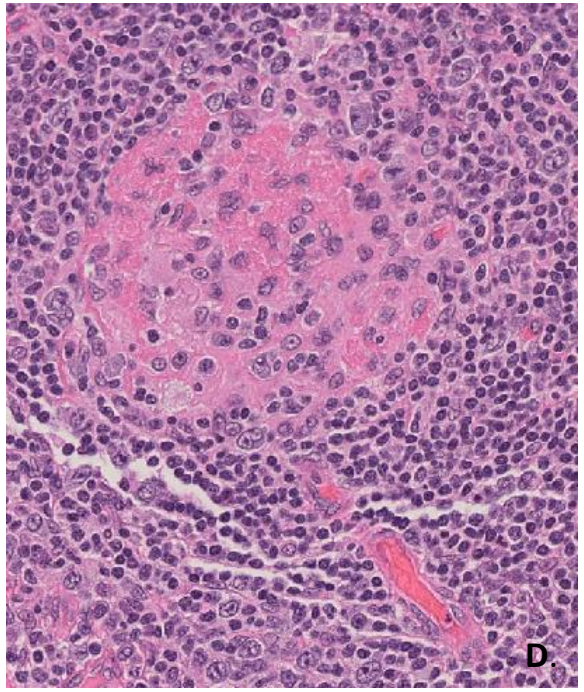

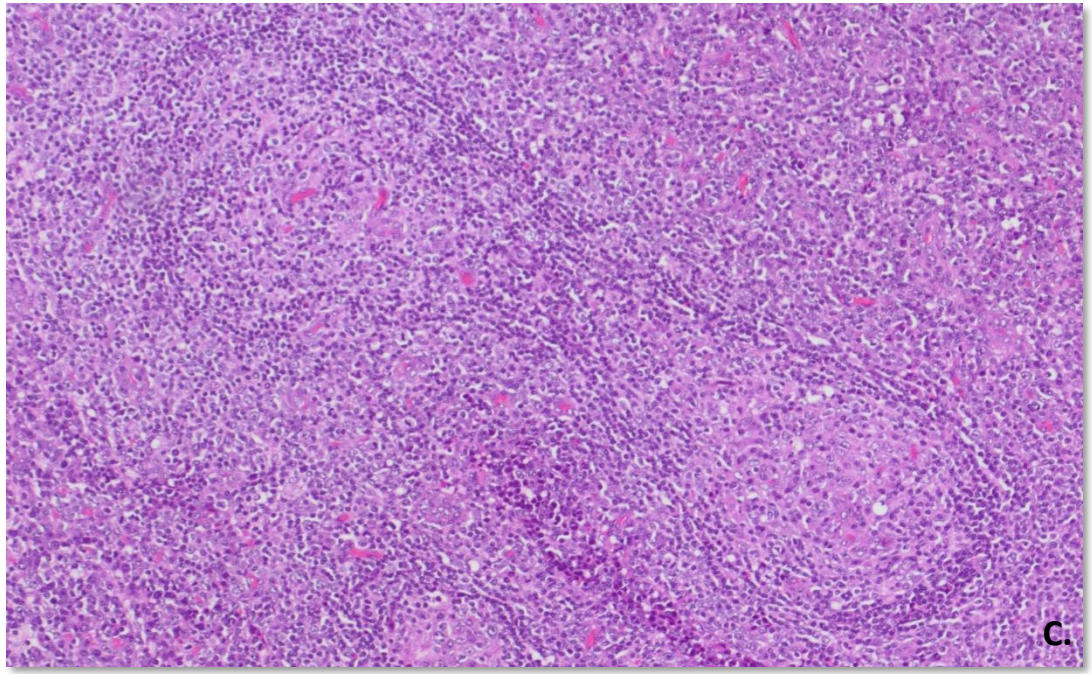

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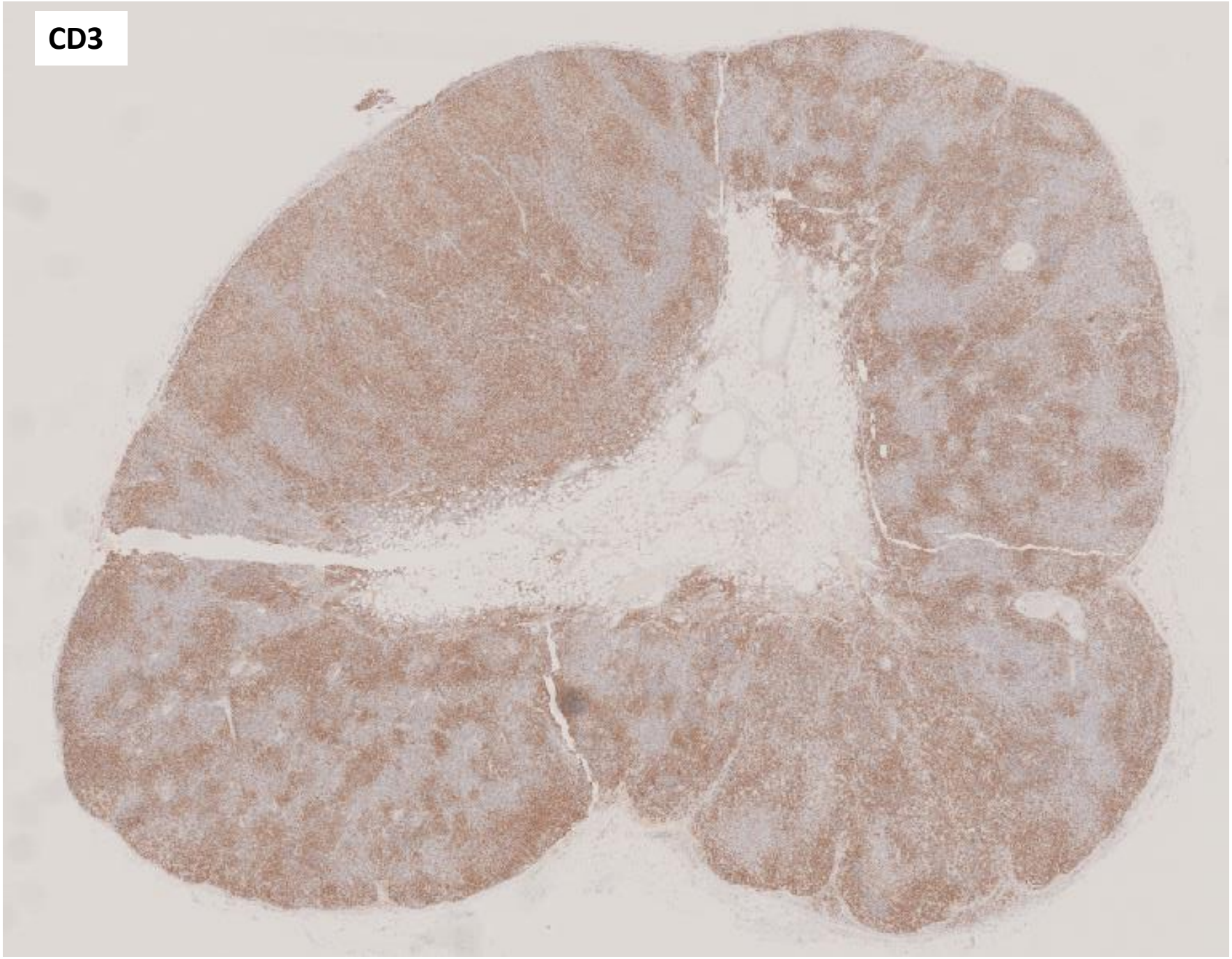

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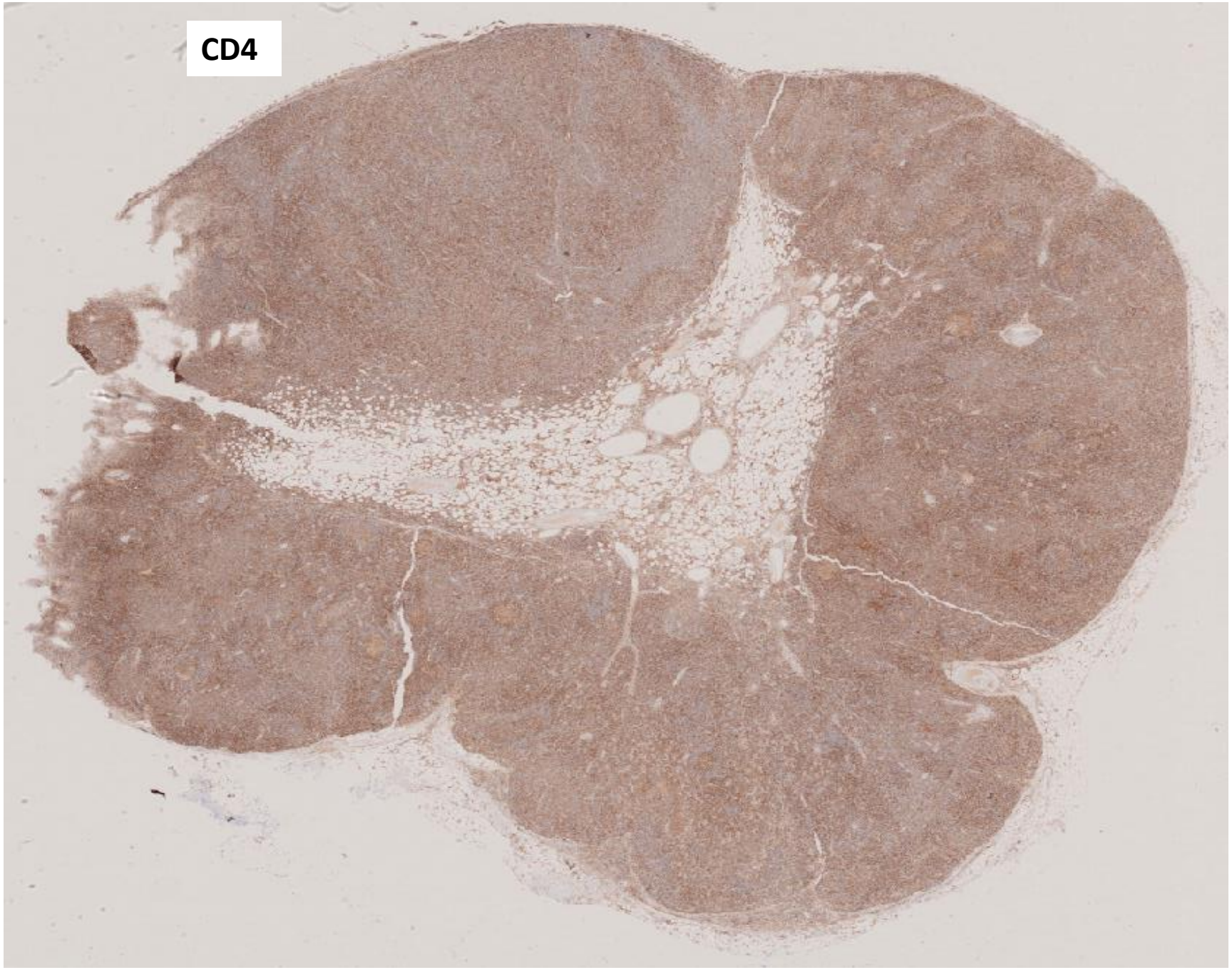

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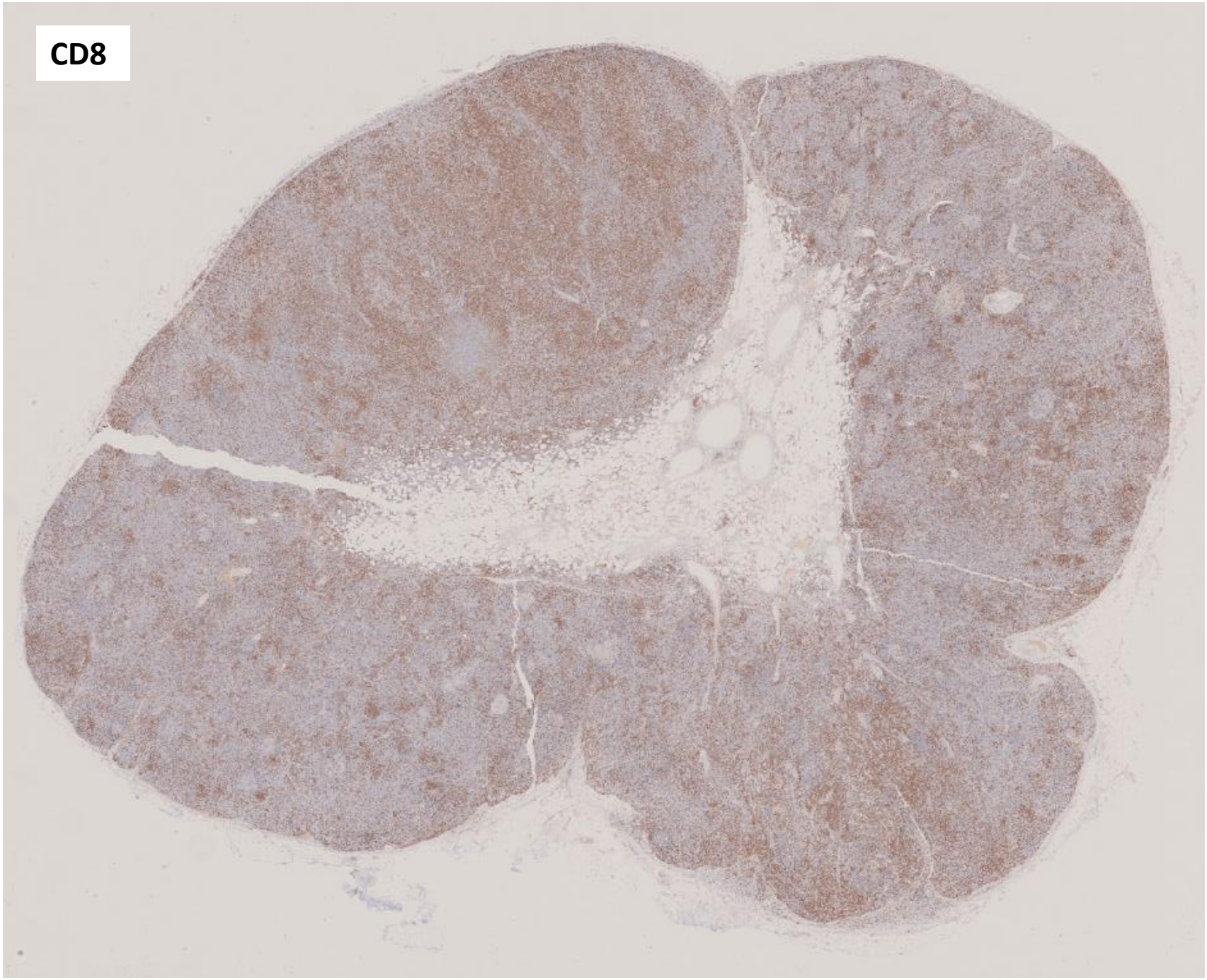

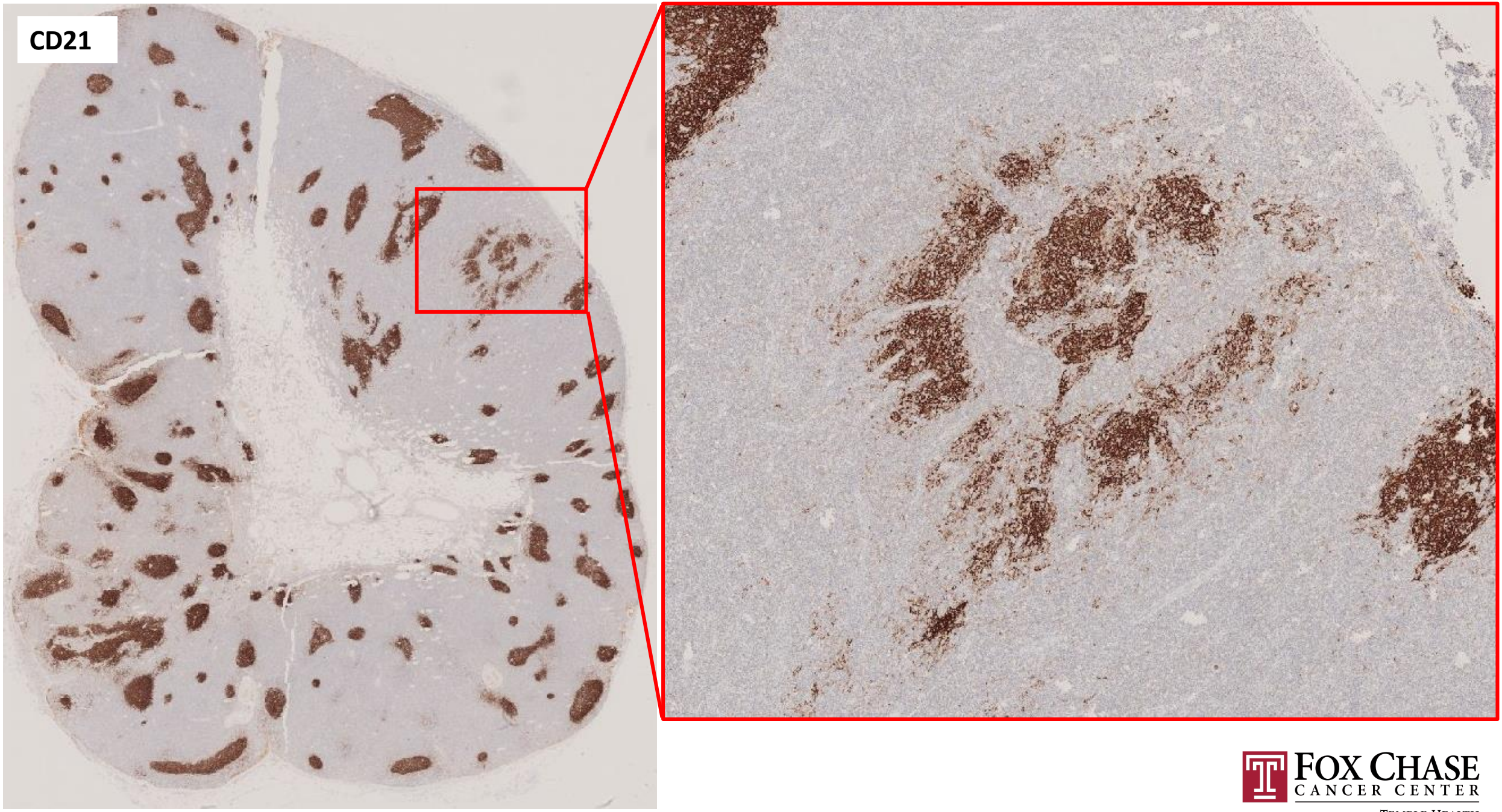

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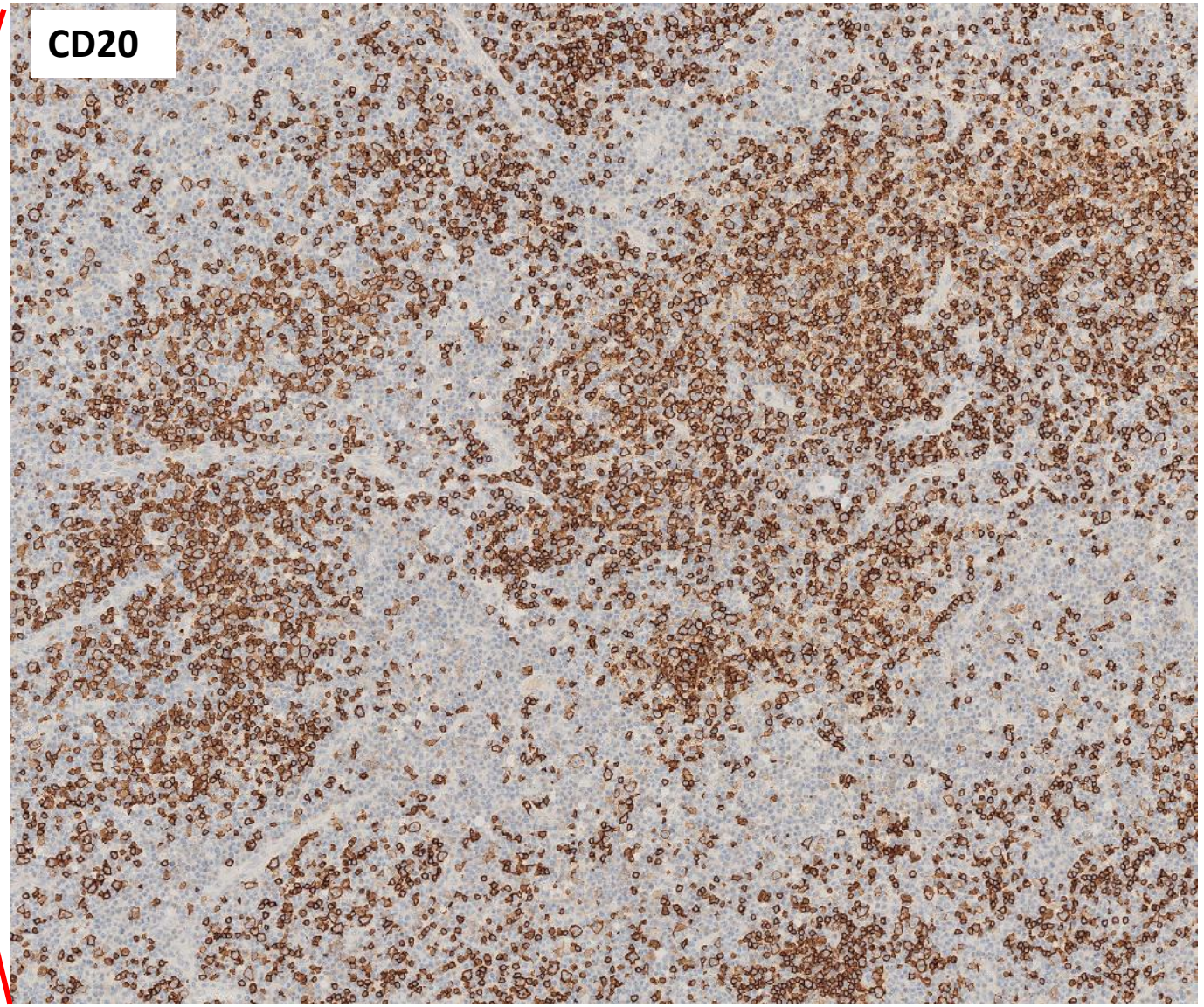

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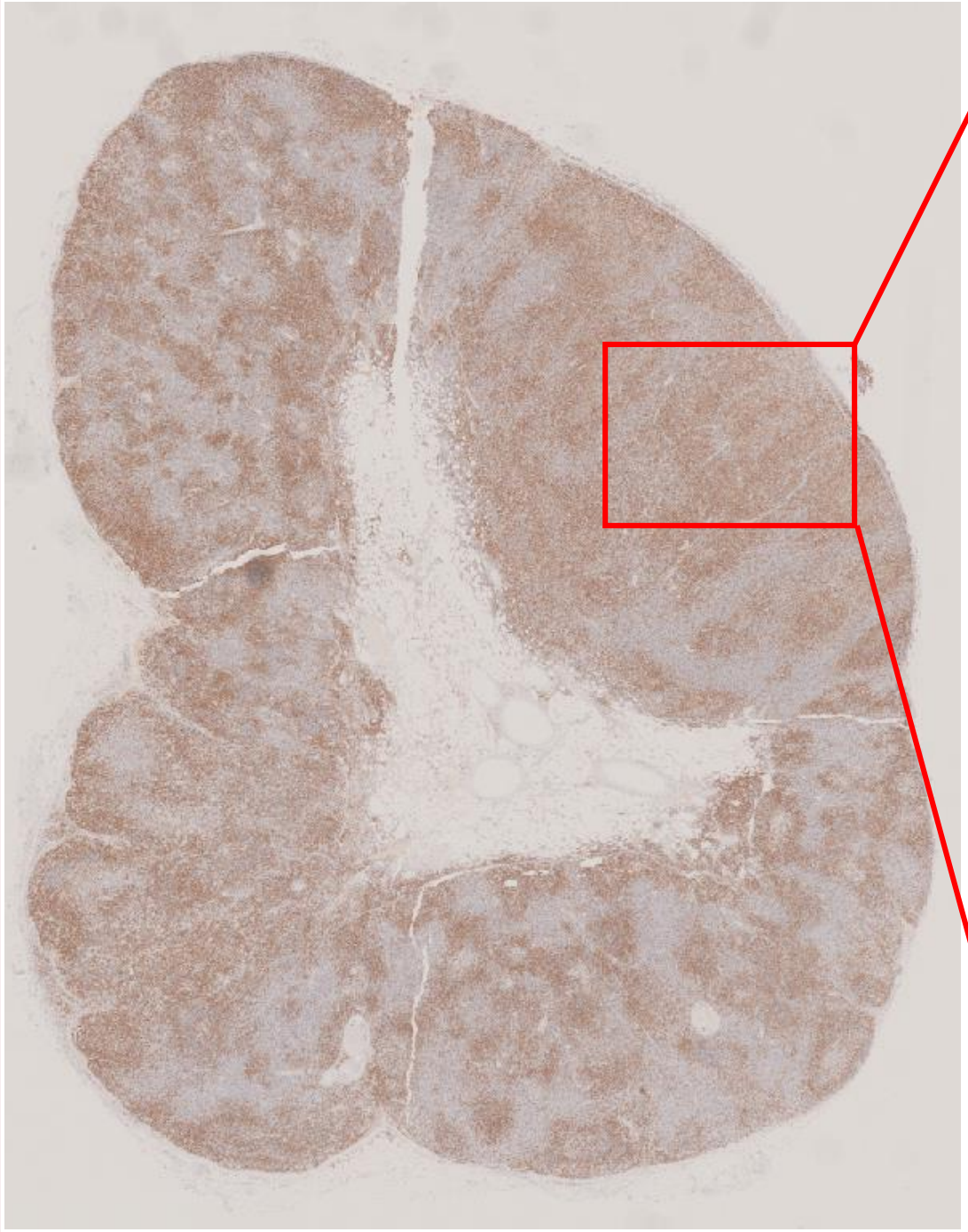

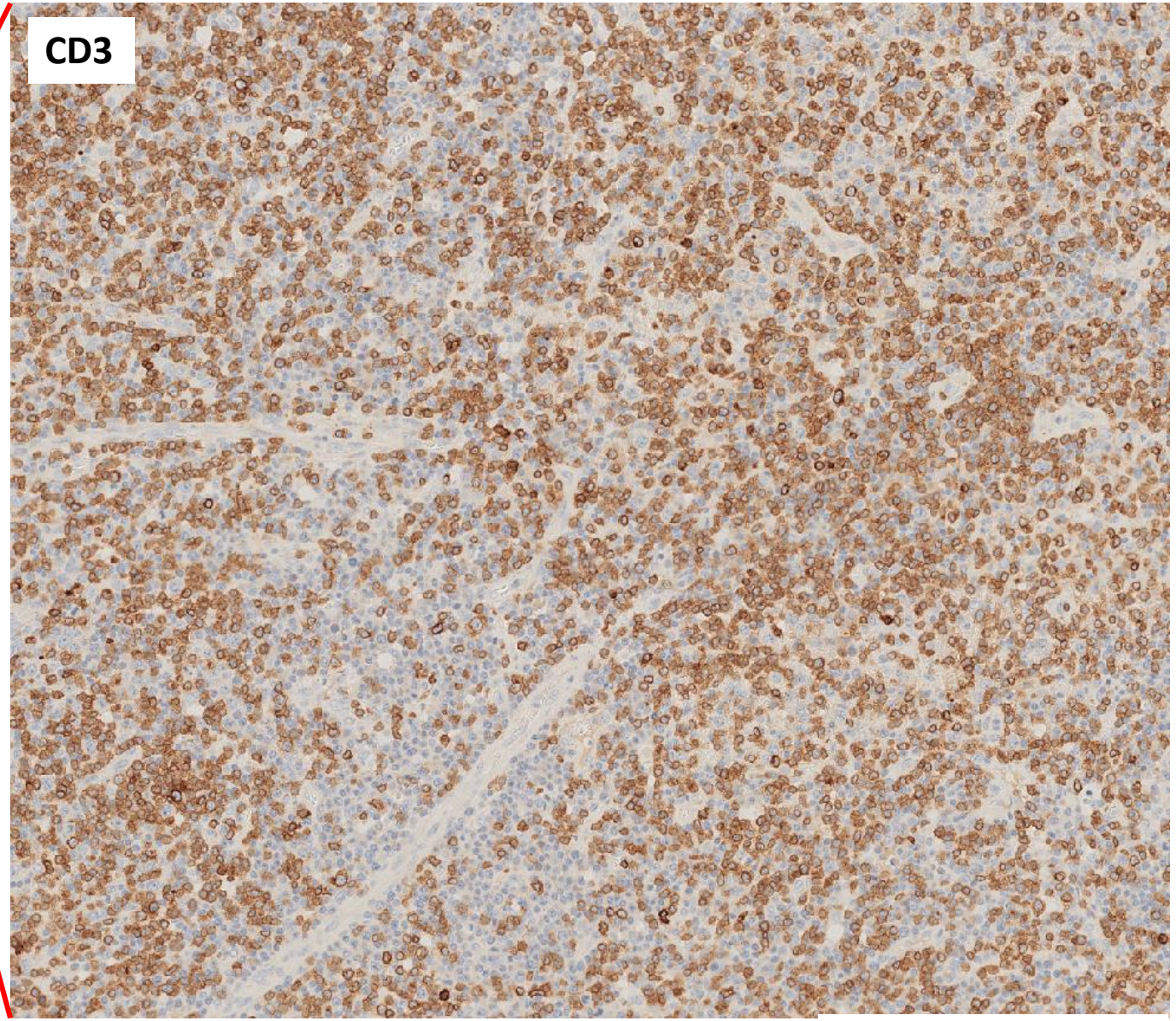

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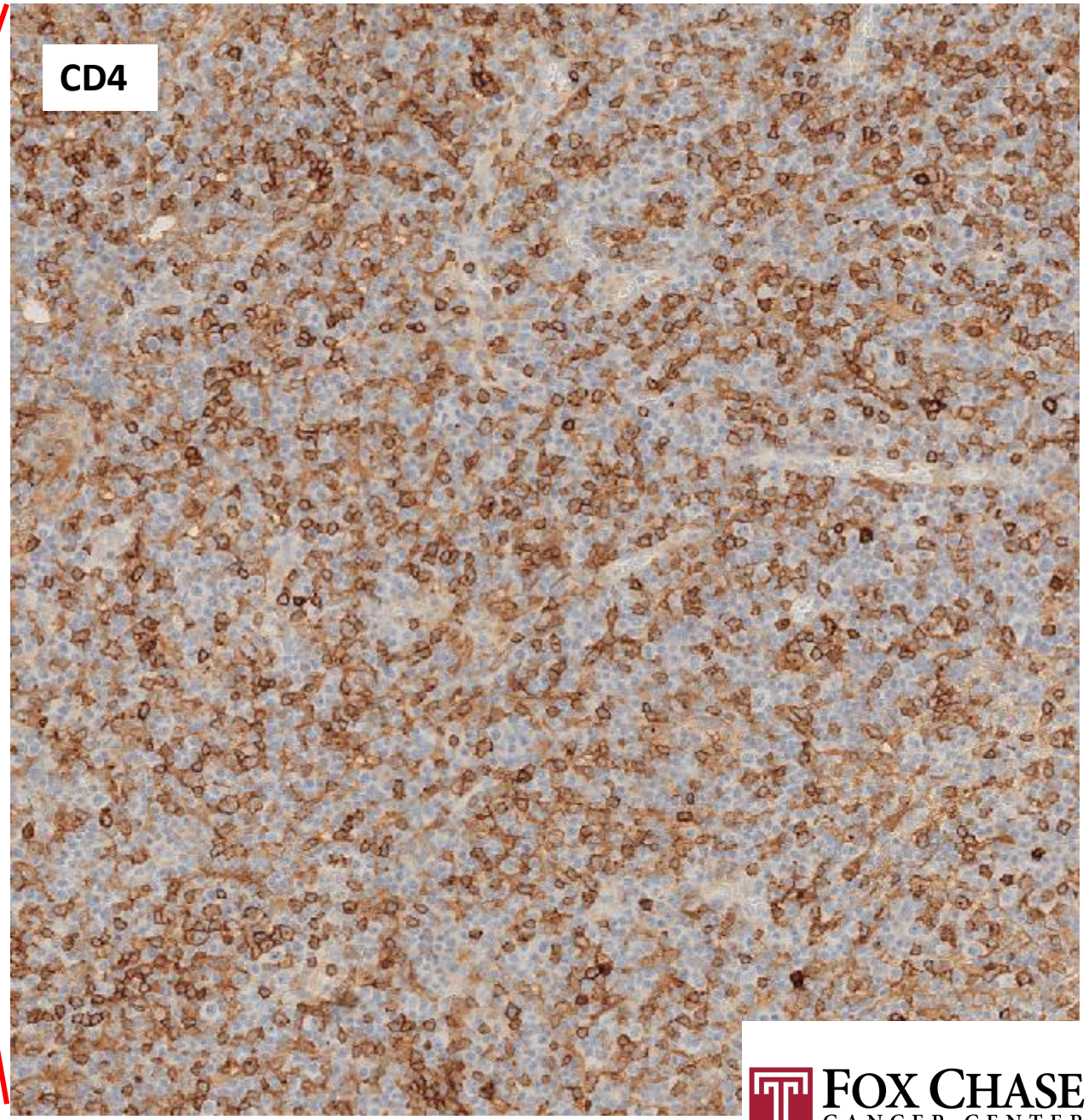

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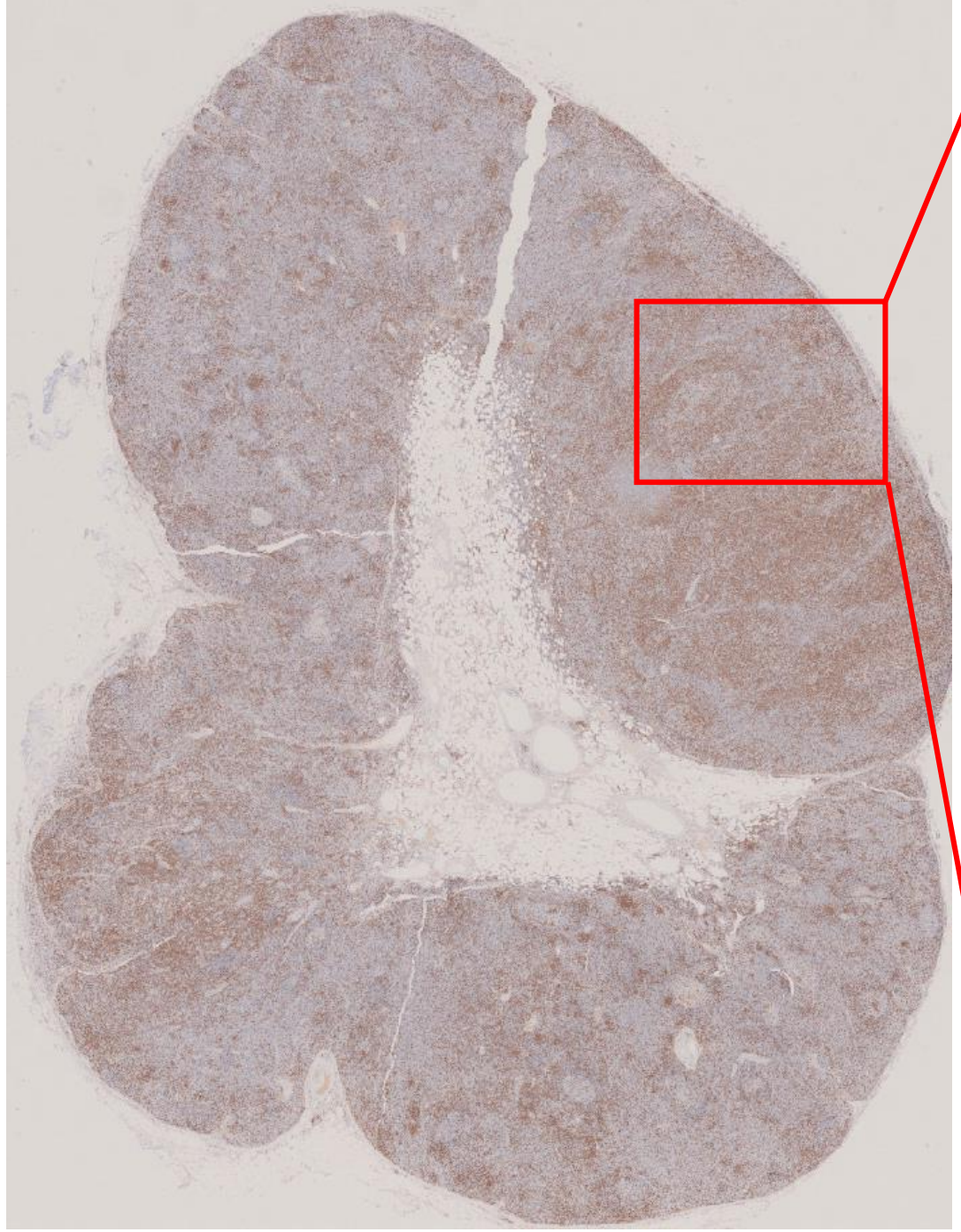

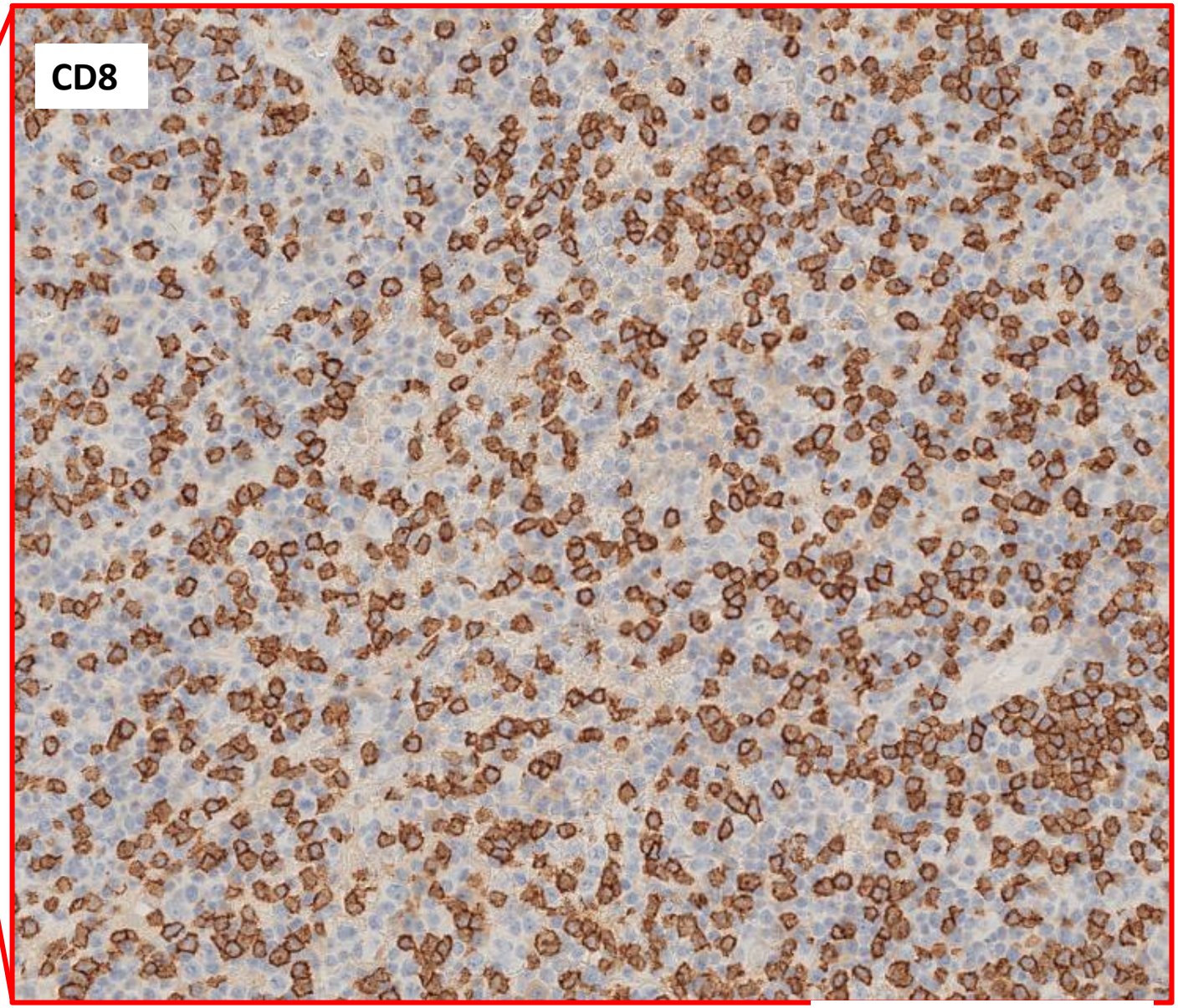

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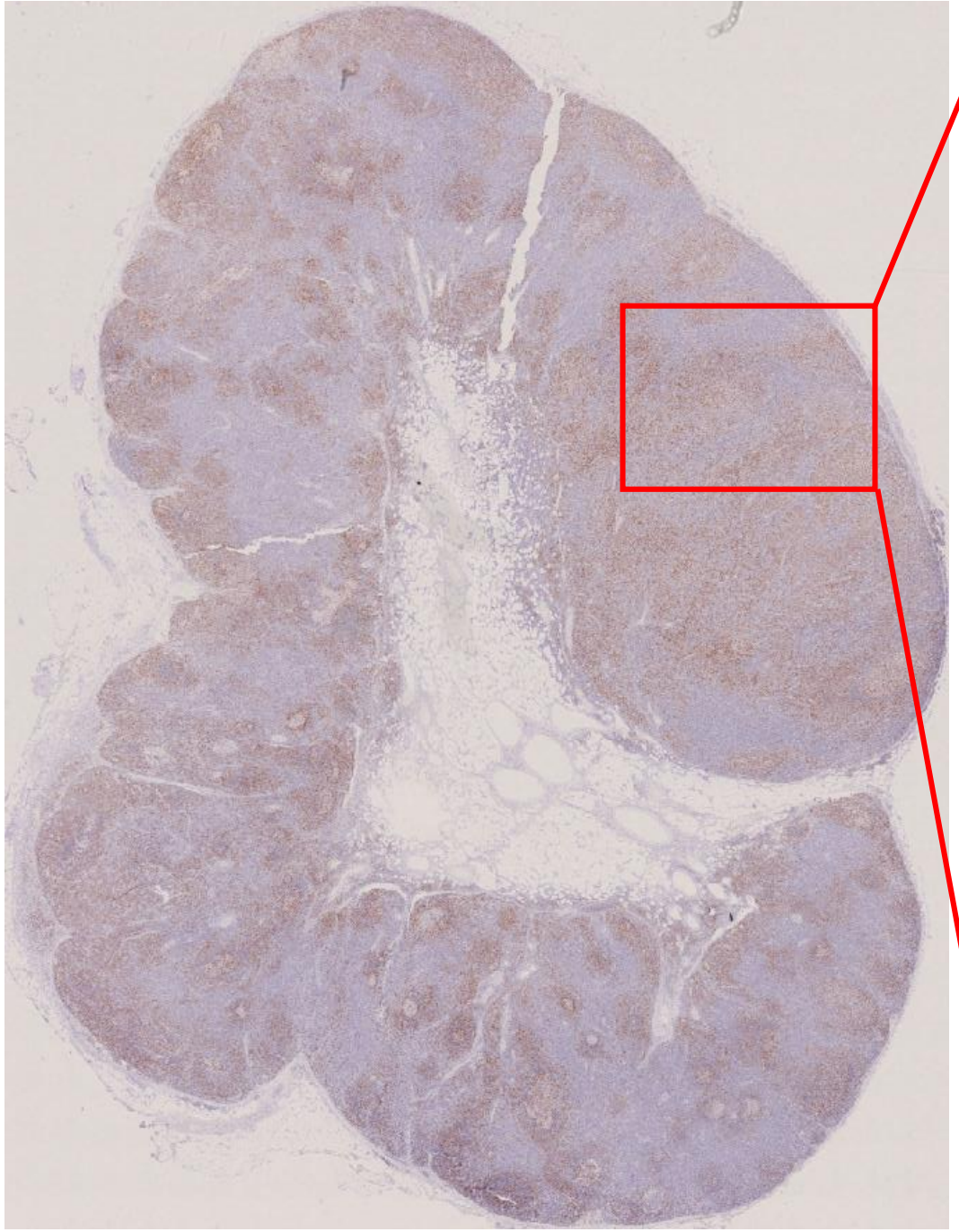
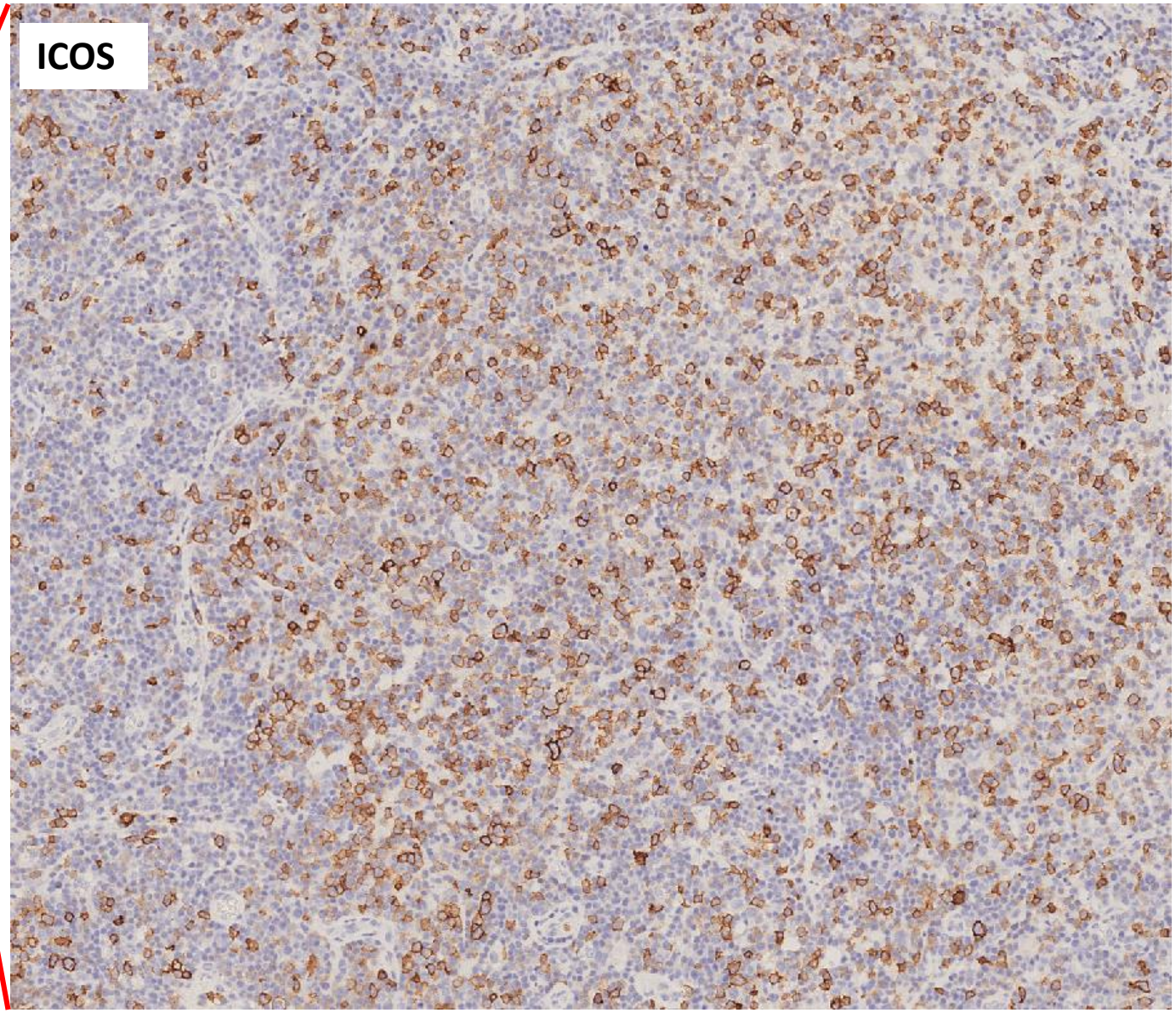
Flow cytometry

1. **Flow cytometry shows no immunophenotypic evidence of clonal B-cell or aberrant T-cell populations.**

Differential diagnosis

1. **Castleman's disease**
2. **Follicular hyperplasia**
3. **Autoimmune diseases (Rheumatoid arthritis, Lymphadenopathy of IgG4-related disease, etc)**
4. **Lymphomas with a nodular component**
5. **POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes)**





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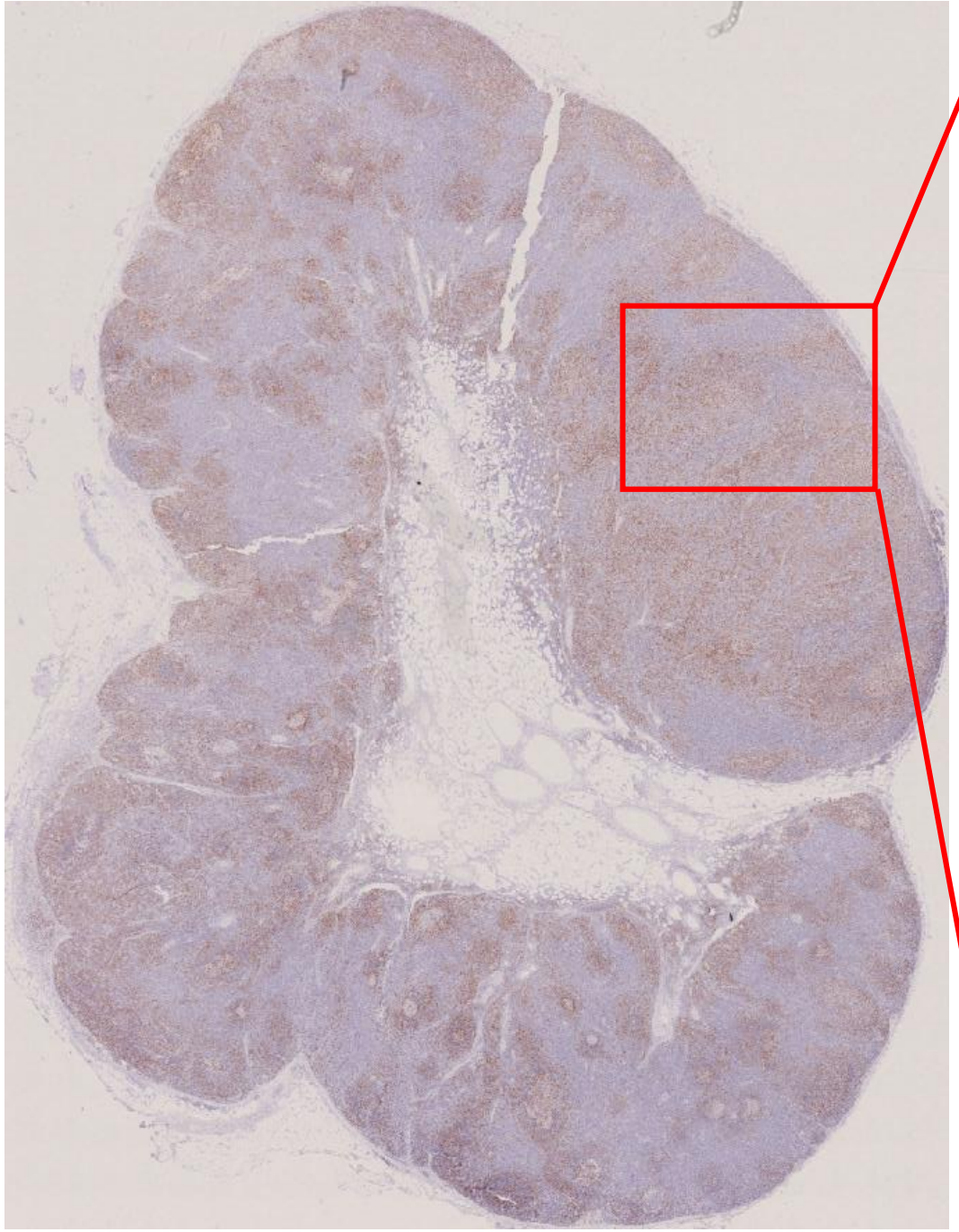

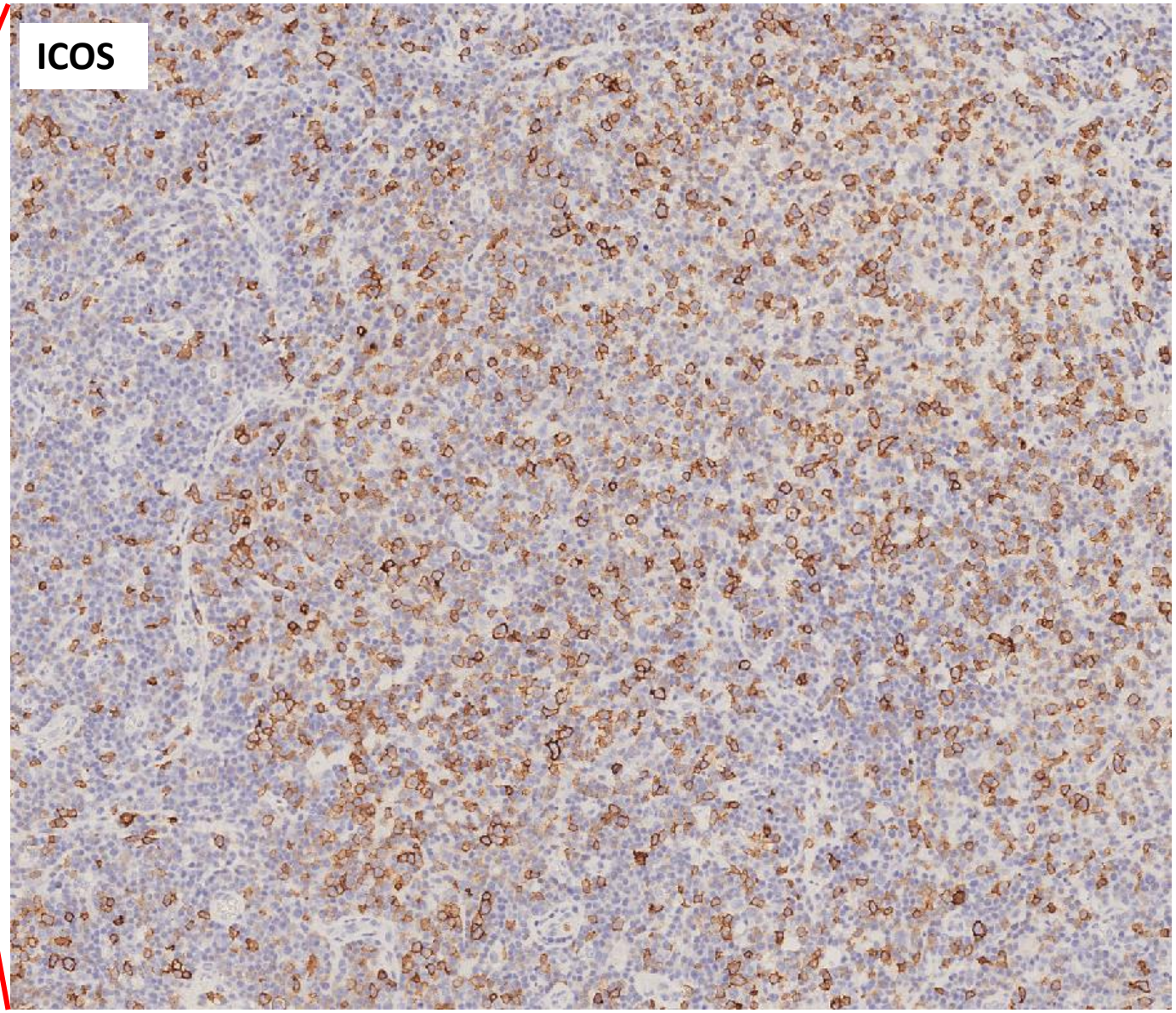

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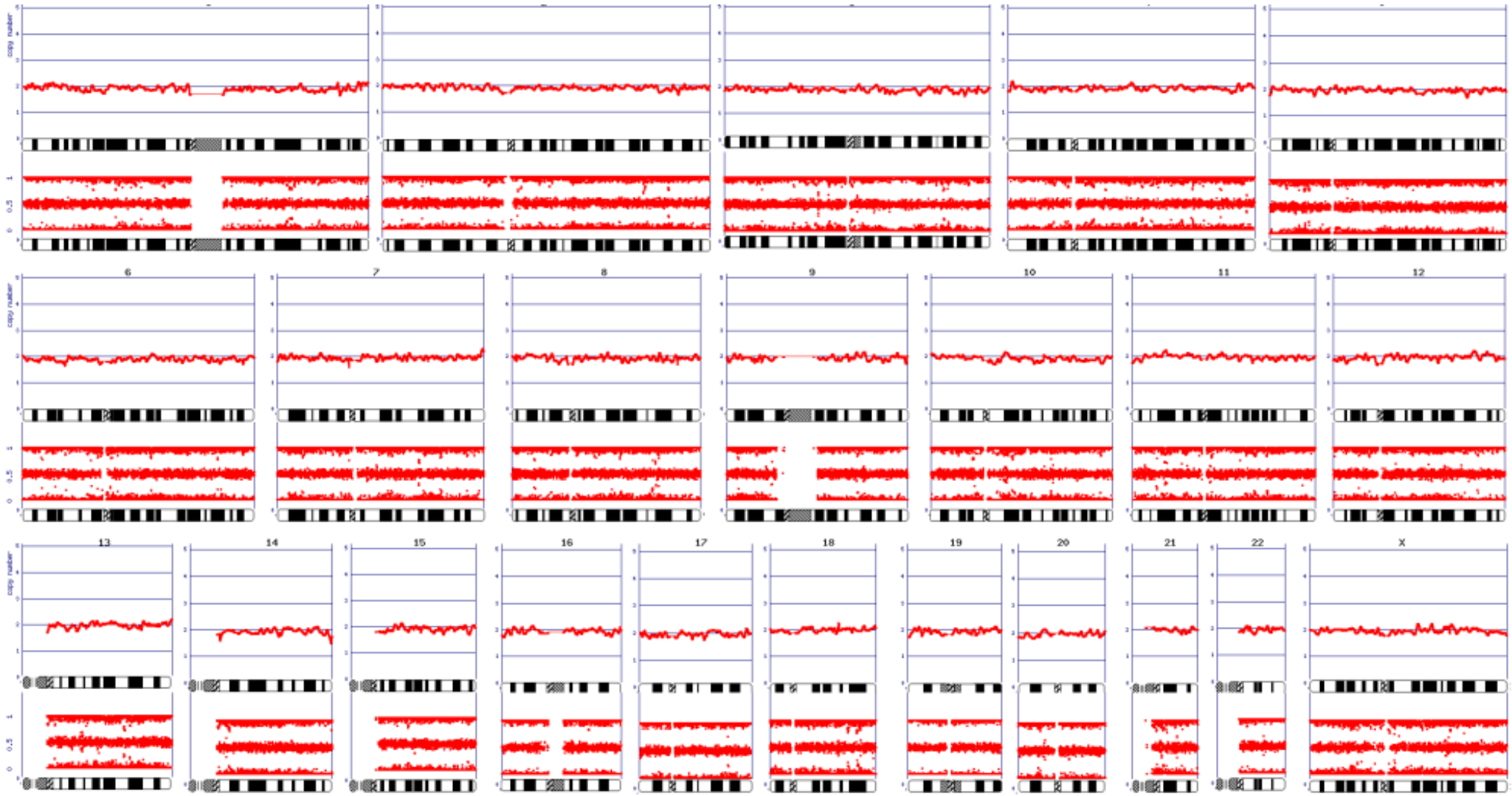
Chromosomal Microarray Analysis:



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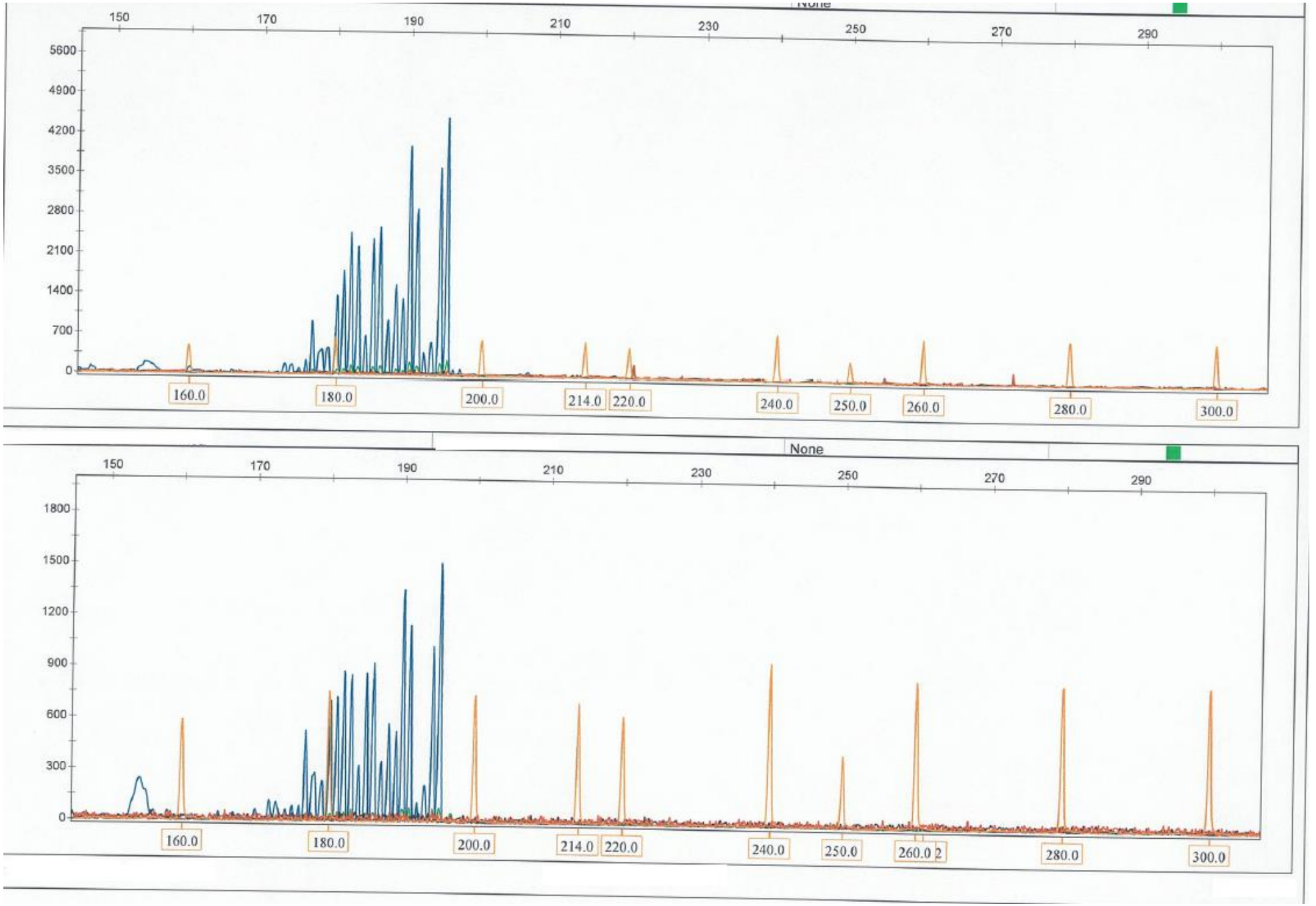

Clonal TCR gene rearrangement

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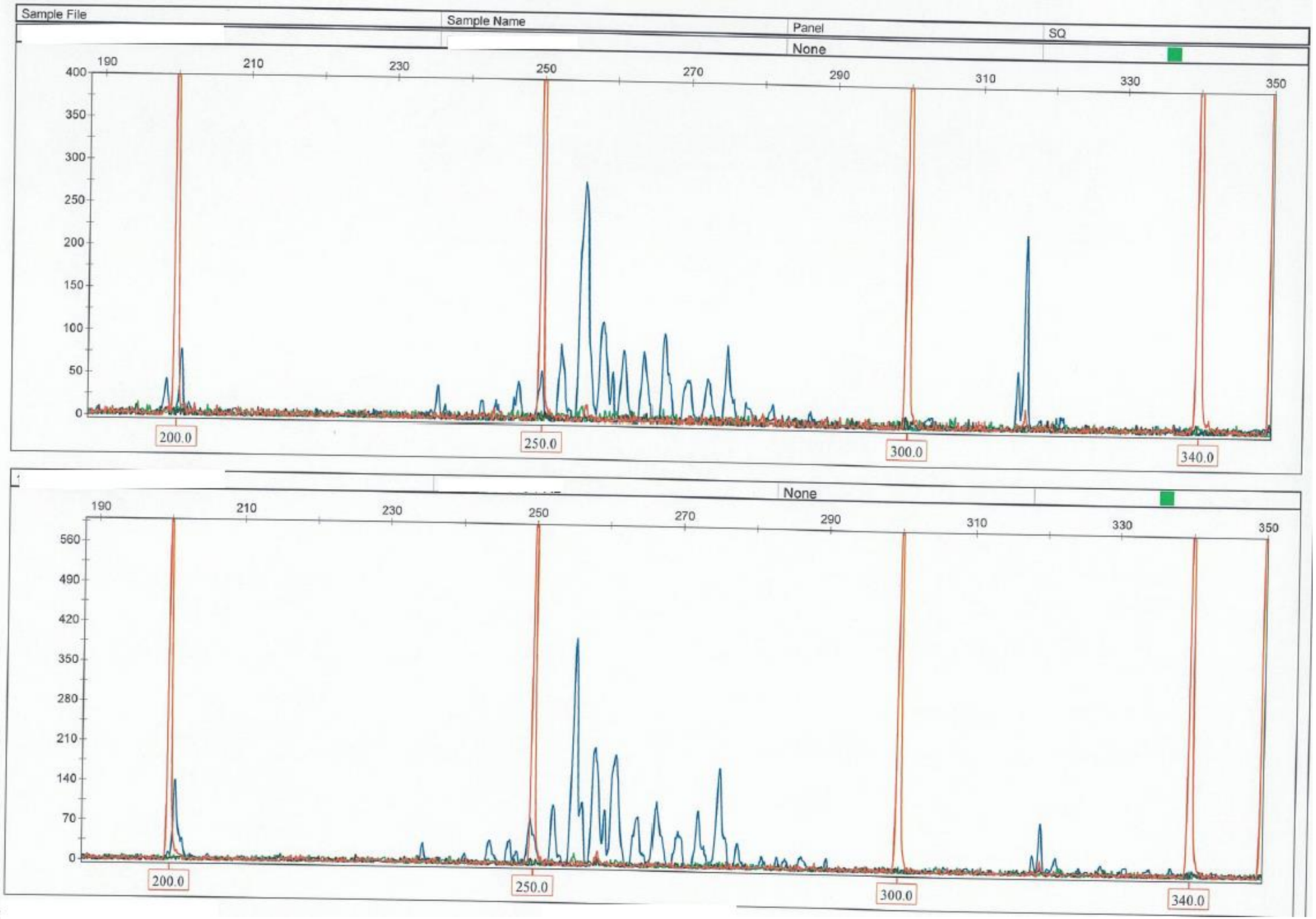

Clonal B-cell gene rearrangement

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Additional studies; Results

Immunohistochemistry	CD4+ T cells: CD5, CD7, **CXCL13 (weaker), ICOS, PD1 and CD10** (Focal interfollicular area) Follicular Dendritic Cells: CD21 and CD23 Plasma Cells: Polyclonal in interfollicular area **EBER positive in scattered cells**				
Chromosomal Micro Array	No abnormal findings				
T-cell (Beta/Gamma) gene rearrangement	**Beta - Positive** **Gamma - Positive**				
B-cell gene rearrangement	**Positive**				
Next Generation Sequencing / Comprehensive Cancer Profile	**Gene**	**Protein Change**	**cDNA Change**	**VAF**	**Tier**
	DNMT3A	p.Arg882His	c.2645G>A	32.6%	Tier 2
	TET2	p.His1219Arg	c.3656A>G	30.6%	Tier 2

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Case 1: Diagnosis

T-follicular helper cell lymphoma with Castleman-like features.

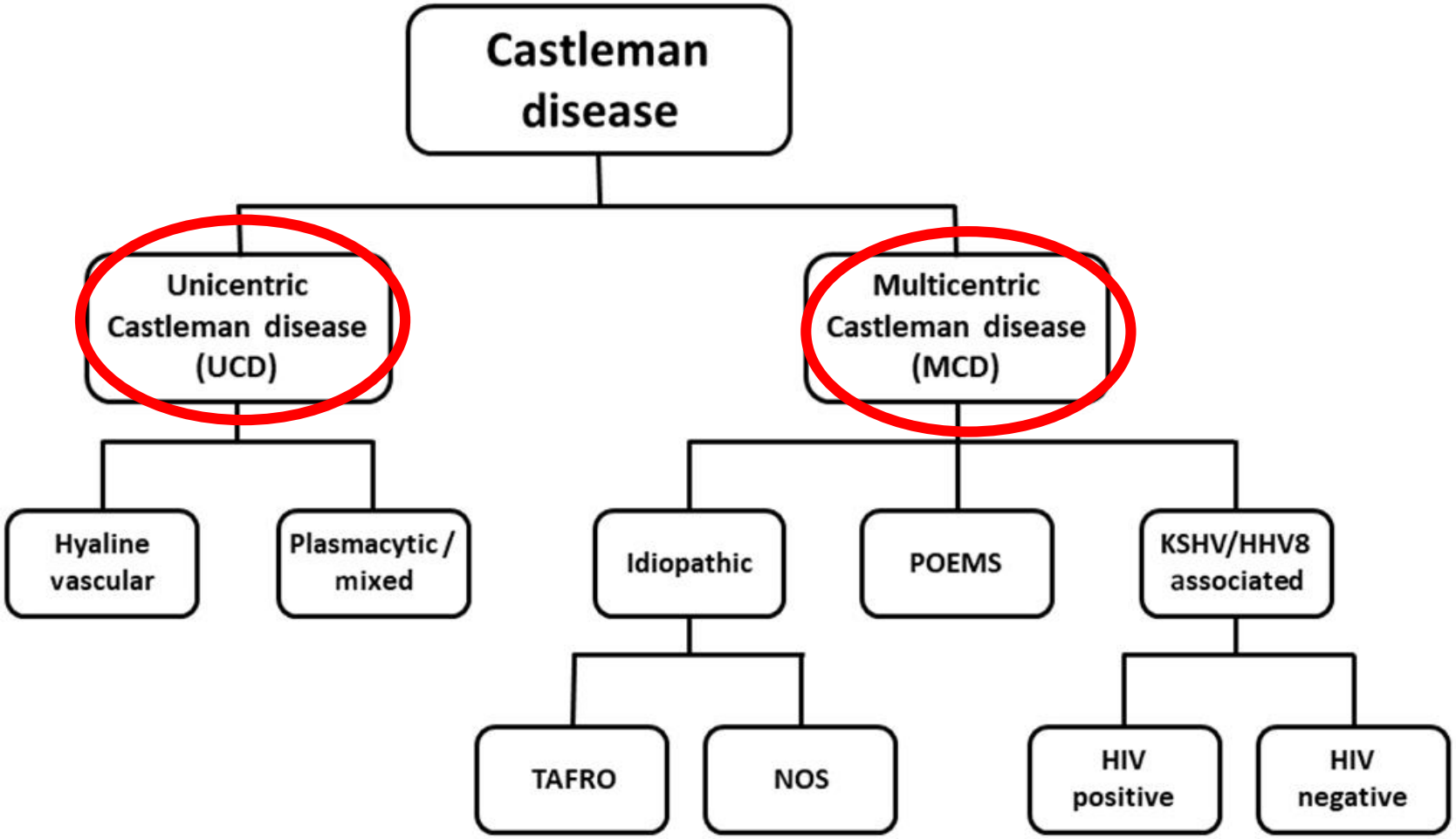
OUTLINE

- Overview of Castleman Disease
- Lymphomas with Castleman-like changes.
- Literature review and case reports

Castleman Disease Overview

- **Definition & Classification**
  - **Castleman disease (CD)** is a group of heterogenous lymphoproliferative disorders
  - Characterized by lymph node enlargement and characteristic histopathological features.

Castleman Disease Overview



Ref: WHO Classification 5th edition

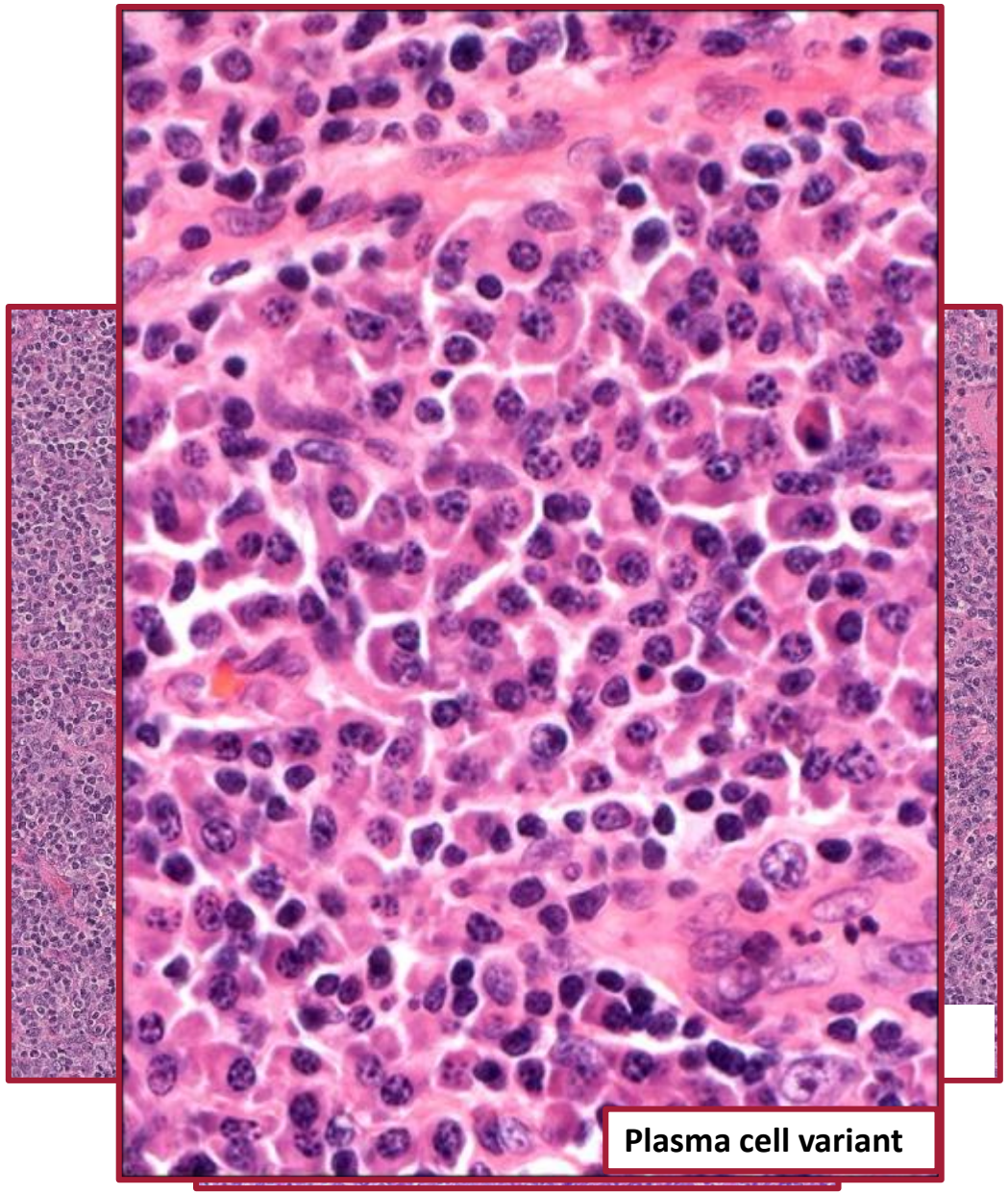
Castleman Disease Overview

- **Clinical Presentation**
  - **UCD**: Localized to a single lymph node station; often asymptomatic, discovered incidentally.
  - **MCD**: Systemic symptoms (fever, weight loss, night sweats), generalized lymphadenopathy, possible organomegaly.
  - **Association with HHV-8**: Particularly in immunocompromised (e.g., HIV).
  - **IL-6 Dysregulation**: Drives inflammatory symptoms, especially in iMCD and HHV-8[1].

1. Sudipto Mukherjee, Rabecka Martin, Brenda Sande, Jeremy S. Paige, David C. Fajgenbaum; Epidemiology and treatment patterns of idiopathic multicentric Castleman disease in the era of IL-6–directed therapy. *Blood Adv* 2022; 6 (2): 359–367. doi: https://doi.org/10.1182/bloodadvances.2021004441

Castleman Disease – Histopathology & Key Features

- **Major Histologic Variants**
  - **Hyaline Vascular (HV) Variant** (most common in UCD)
    - **"Onion-skin"**: Mantle zone hyperplasia with concentric layering of lymphocytes.
    - **"Lollipop" sign**: Germinal centers atrophic follicles with hyalinized vessels.
    - **"Twinning"**: two germinal centers appear within a single follicle.
  - **Plasma Cell (PC) Variant** (commonly seen in MCD)
    - Expanded interfollicular regions with sheets of plasma cells.
    - Follicles may be less regressed; not as hyalinized.
  - **Mixed Variant**: Features of both HV and PC patterns.



Castleman Disease – Histopathology & Key Features

- **Immunophenotype & Ancillary Studies**
  - **Immunostain for B-cell in follicles** and T cells in the interfollicular areas.
  - **HHV-8 testing** (e.g., LANA-1 staining) in suspected MCD-HHV8.
  - **Serum IL-6** can be elevated in iMCD.
  - **Germline mutations** of NCOA4 and TRAF [1]

1. Frits van Rhee, David Fajgenbaum; Insights into the etiology of Castleman disease. Blood 2024; 143 (18): 1789–1790. doi: https://doi.org/10.1182/blood.2023023716

Castleman Disease – Histopathology & Key Features

- **Immunophen**
  - **Immunostai** licular areas.
  - **HHV-8 testin** V8.
  - **Serum IL-6** c
  - **Germline mu**

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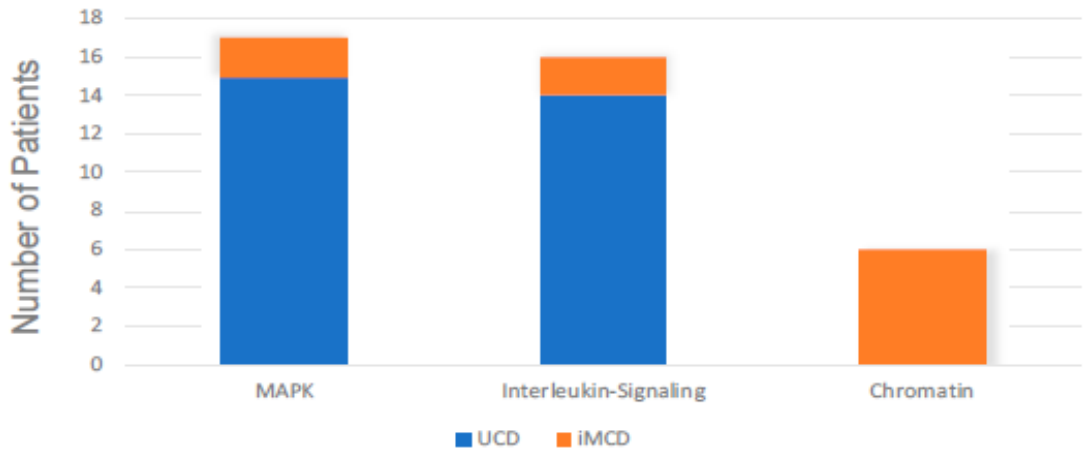


B

Pathways	UCD	iMCD
MAPK pathway	*FAS, PDGFRB, FGFR3, NF1, IL6ST, HRAS, KRAS, NRAS, ERBB4, JAK3, BRAF and TGFBR2*	*PTPRR, ERBB2, FAS, STK3, TGFBR2*
Interleukin signaling pathway	*PDGFRB, FGFR3, NF1, PIM1, PTPN6, IL6ST, JAK1, HRAS, KRAS, NRAS, JAK2, AKT1, ERBB4, JAK3*	*ERBB2, JAK2, PTPN6*
Chromatin remodeling	none	*SETD1A, ASH1L, DOT1L, JAK2, KMT2E, DNMT3A*

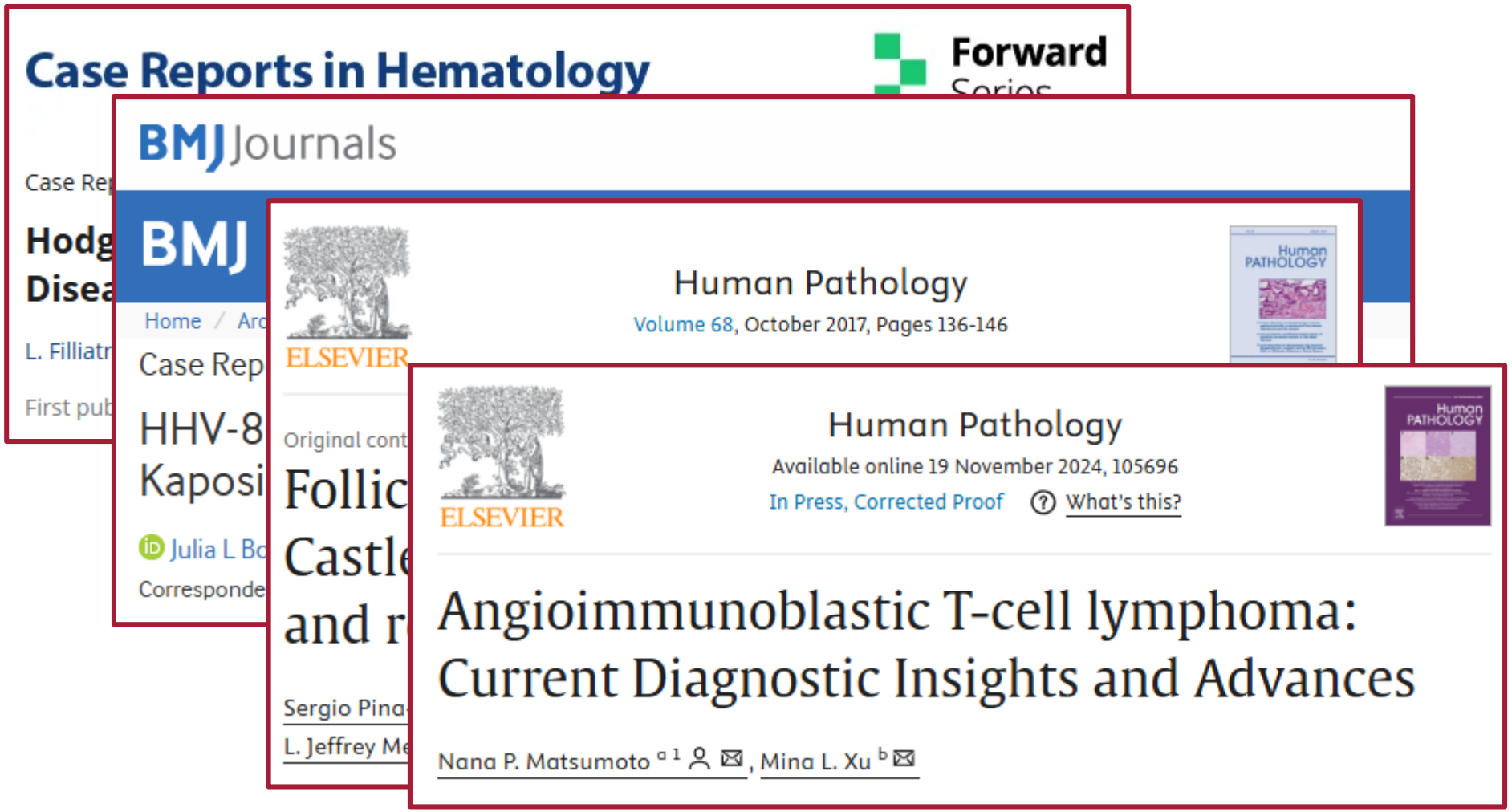
1. Frits van Rhee, David Fajgenbaum; Insights into the etiology of Castleman disease. Blood 2024; 143 (18): 1789–1790. doi: https://doi.org/10.1182/blood.2023023716

Castleman-like Lymphoma Changes – Context & Overview

- **Definition & Clinical Context**
  - **"Castleman-like" changes** refer to lymph node architecture resembling Castleman disease but associated with a lymphoma or lymphoproliferative disorder.
  - Found in various malignant settings, e.g.:
    - Hodgkin lymphoma (particularly nodular sclerosis type)
    - Peripheral T-cell lymphomas
    - T-cell/histiocyte-rich large B-cell lymphoma
    - Can occur in the same node as or adjacent to neoplastic foci.
  - Often related to local cytokine production (e.g., IL-6), similar to Castleman disease [1-3].

1. Alex Reza Gholiha, Peter Hollander, Ingrid Glimelius, Gustaf Hedstrom, Daniel Molin, Henrik Hjalgrim, Karin E. Smedby, Jamileh Hashemi, Rose-Marie Amini, Gunilla Enblad; Revisiting IL-6 expression in the tumor microenvironment of classical Hodgkin lymphoma. Blood Adv 2021; 5 (6): 1671–1681. doi: https://doi.org/10.1182/bloodadvances.2020003664
2. Bao C, Gu J, Huang X, You L, Zhou Z, Jin J. Cytokine profiles in patients with newly diagnosed diffuse large B-cell lymphoma: IL-6 and IL-10 levels are associated with adverse clinical features and poor outcomes. Cytokine. 2023 Sep;169:156289. doi: 10.1016/j.cyto.2023.156289. Epub 2023 Jul 13. PMID: 37453327.
3. The IL-6 signaling complex is a critical driver, negative prognostic factor, and therapeutic target in diffuse large B-cell lymphoma. Hind Hashwah, Katrin Bertram, Kristin Stirm, Anna Stelling, Cheuk-Ting Wu, Sabrina Kasser, Markus G Manz, Alexandre P Theocharides, Alexandar Tzankov, and Anne Müller https://orcid.org/0000-0002-1368-8276 mueller@imcr.uzh.ch. EMBO Mol Med (2019) 11: e10576 https://doi.org/10.15252/emmm.201910576

Castleman Like lymphomas literature review and case reports



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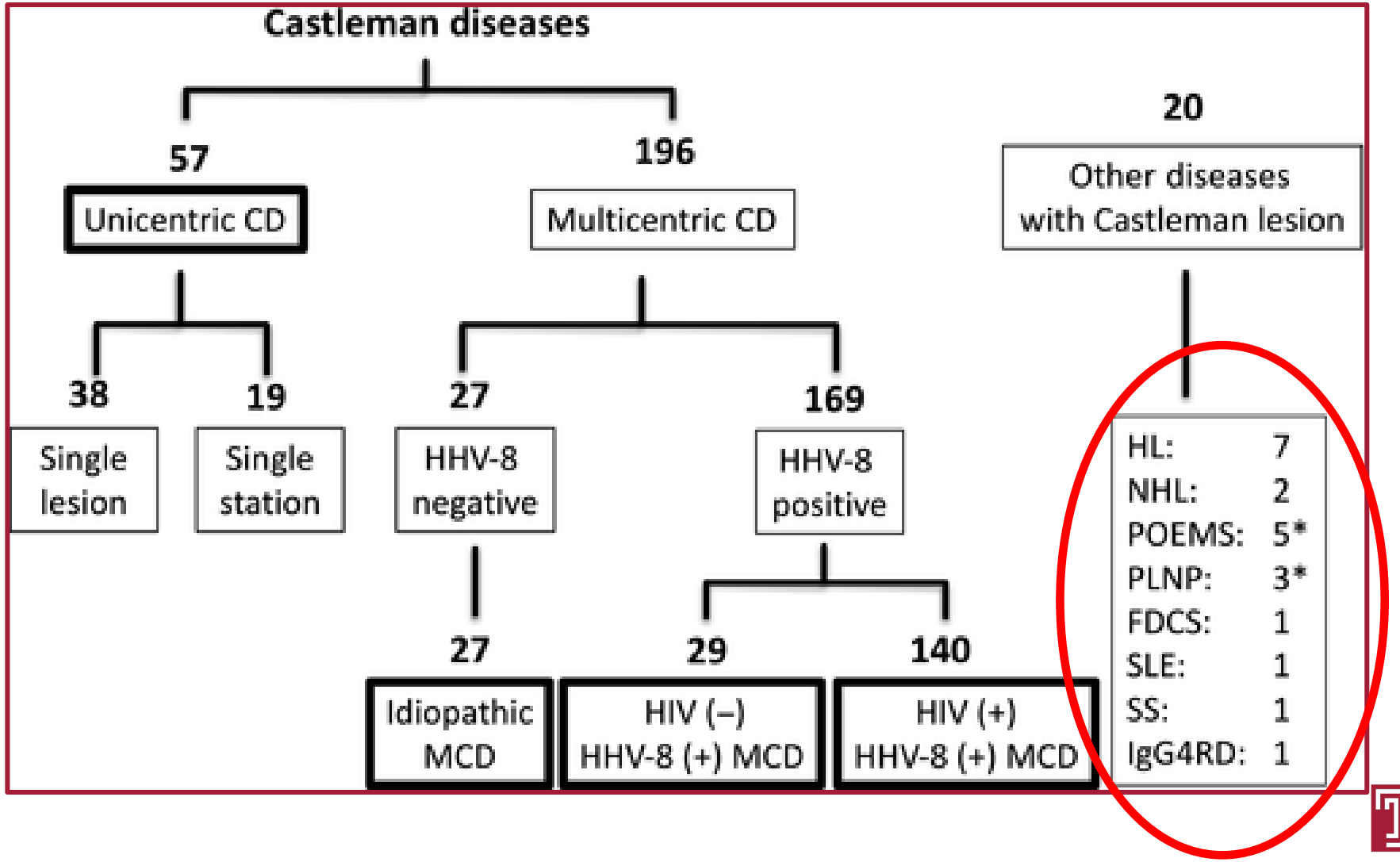
Castleman Like lymphomas literature review and case reports



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Summary of case reports for Castleman Like lymphomas case reports

References
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Concurrent HHV-8–Associated Multicentric Castleman Disease & Hodgkin Lymphoma. Boland JL, et al. 2022 Sep 5;15(9):e250228. doi: 10.1136/bcr-2022-250228. PMID: 39901380; PMCID: PMC9445794.
Follicular lymphoma with hyaline-vascular Castleman-like features: analysis of 6 cases and review of the literature. Pina-Oviedo S, et. al. Hum Pathol. 2017 Oct;68:136-146. doi: 10.1016/j.humpath.2017.08.024. Epub 2017 Sep 2. PMID: 28873356.
Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Soulier J, et. al. Blood. 1995 Aug 15;86(4):1276-80. PMID: 7632932.
High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. Oksenhendler E, et. al. Blood. 2002 Apr 1;99(7):2331-6. doi: 10.1182/blood.v99.7.2331. PMID: 11895764.
HHV8-related lymphoid proliferations: a broad spectrum of lesions from reactive lymphoid hyperplasia to overt lymphoma. Gonzalez-Farre B, et. al. Mod Pathol. 2017 May;30(5):745-760. doi: 10.1038/modpathol.2016.233. Epub 2017 Jan 13. PMID: 28084335.
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The full spectrum of Castleman disease: 273 patients studied over 20 years. Oksenhendler E, et. al. Br J Haematol. 2018 Jan;180(2):206-216. doi: 10.1111/bjh.15019. Epub 2017 Nov 16. PMID: 29143319.

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Distinguishing Castleman-like Changes from Castleman Disease

- **Histopathological Pitfalls**
  - **Focal vs. Diffuse**: In true Castleman disease, changes are typically diffuse and dominate the lymph node architecture. “Castleman-like” foci may be patchy or overshadowed by neoplastic areas.
  - **Cytologic Atypia**: Lymphomas will show cytologically atypical lymphoid populations or Reed-Sternberg cells (in Hodgkin lymphoma).
  - **Peripheral T-cell Lymphoma**: May show aberrant T-cell immunophenotype, clonality, or infiltration pattern that is not typical of Castleman disease.

Distinguishing Castleman-like Changes from Castleman Disease

- **Diagnostic Approach**
  - **Thorough Node Sampling**: Evaluate multiple areas to assess distribution of Castleman-like features vs. neoplastic infiltration.
  - **Immunophenotypic & Molecular Studies**:
    - B-cell clonality (e.g., IgH rearrangements).
    - T-cell receptor gene rearrangements (in suspected T-cell lymphoma).
    - HHV-8 LANA-1 staining if MCD-HHV8 is in the differential.
  - **Correlation with Clinical & Laboratory Findings**:
    - Systemic “B” symptoms, organomegaly, abnormal labs (LDH, CBC, etc.).

Conclusion

- Castleman disease is a diagnosis of exclusion
- Must rule out other entities with Castleman-like features including lymphomas
- Potential topic of investigation and collaboration

Thank you!

Multi-Institutional Hematopathology Case Presentation

A Special thanks to Drs. Wasik, Nejati, Mackrides for mentorship

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