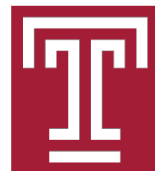




Monthly Multi-Institutional Hematopathology Interesting Case Conference

with **Fahad S. Ahmed, MD.**
Hematopathology Fellow
Fox Chase Cancer Center
Philadelphia, PA

2/26/2025



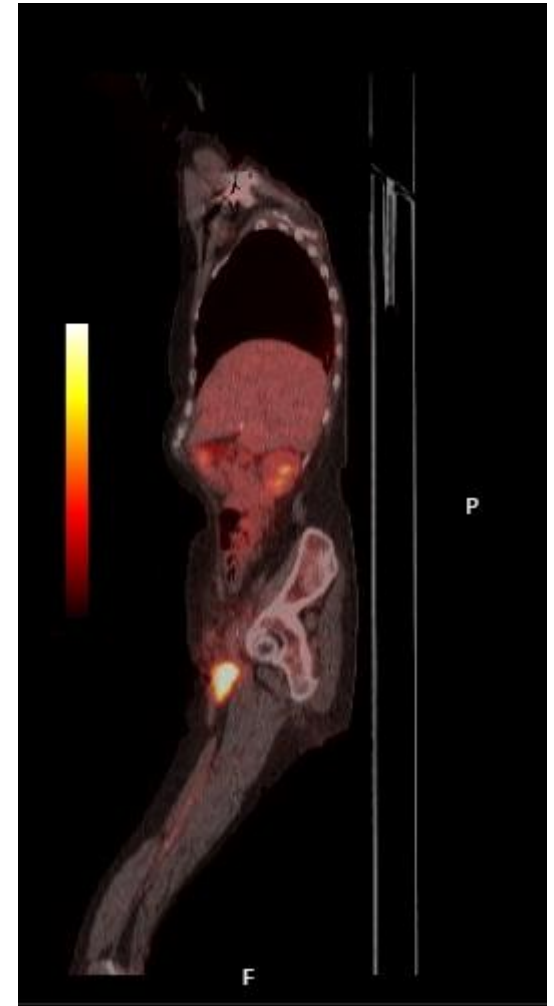
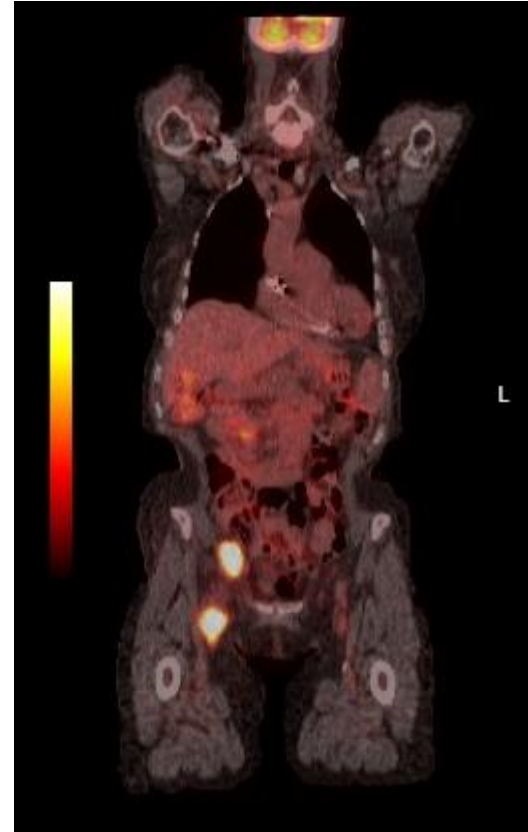
FOX CHASE
CANCER CENTER

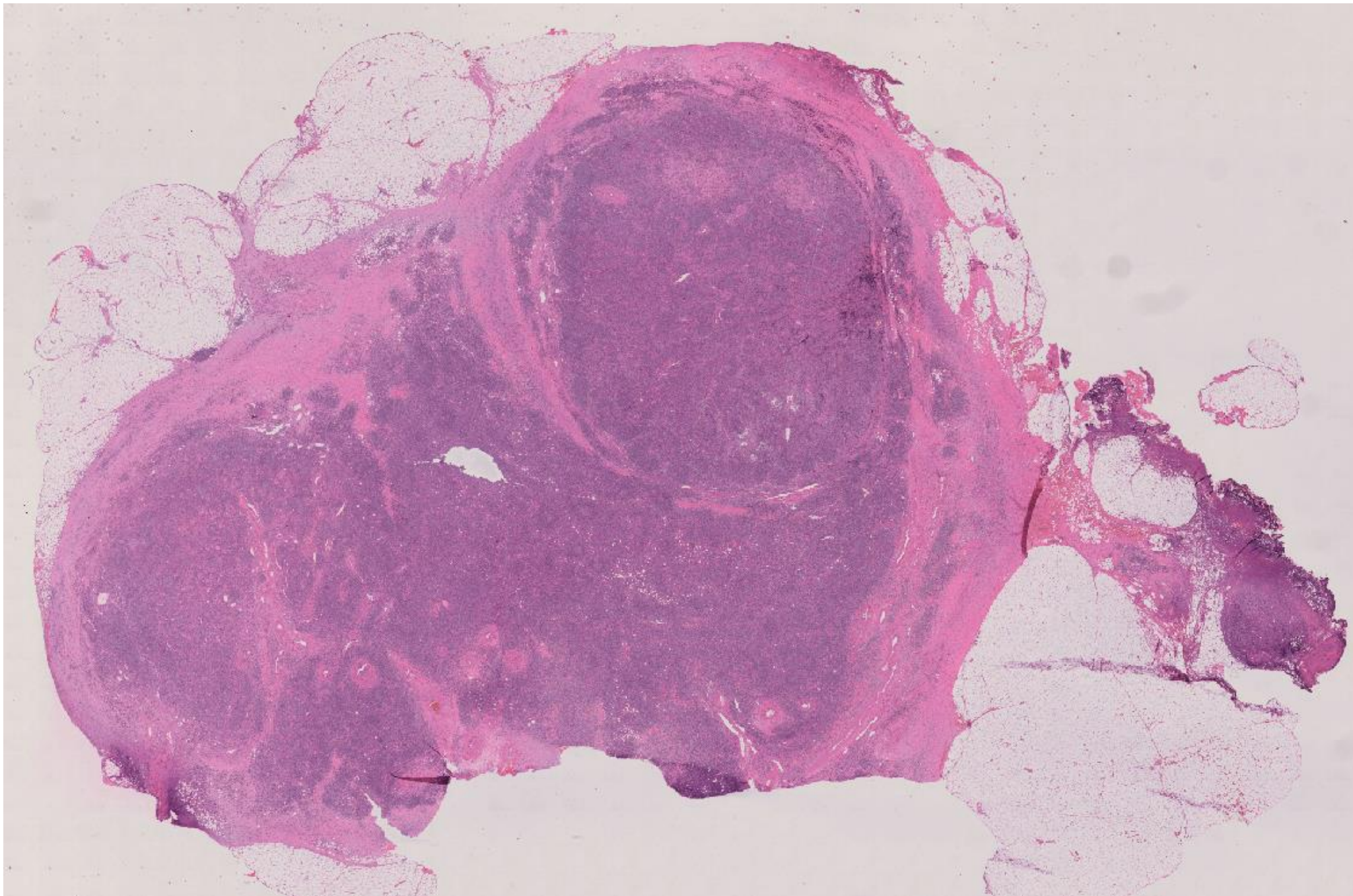
TEMPLE HEALTH

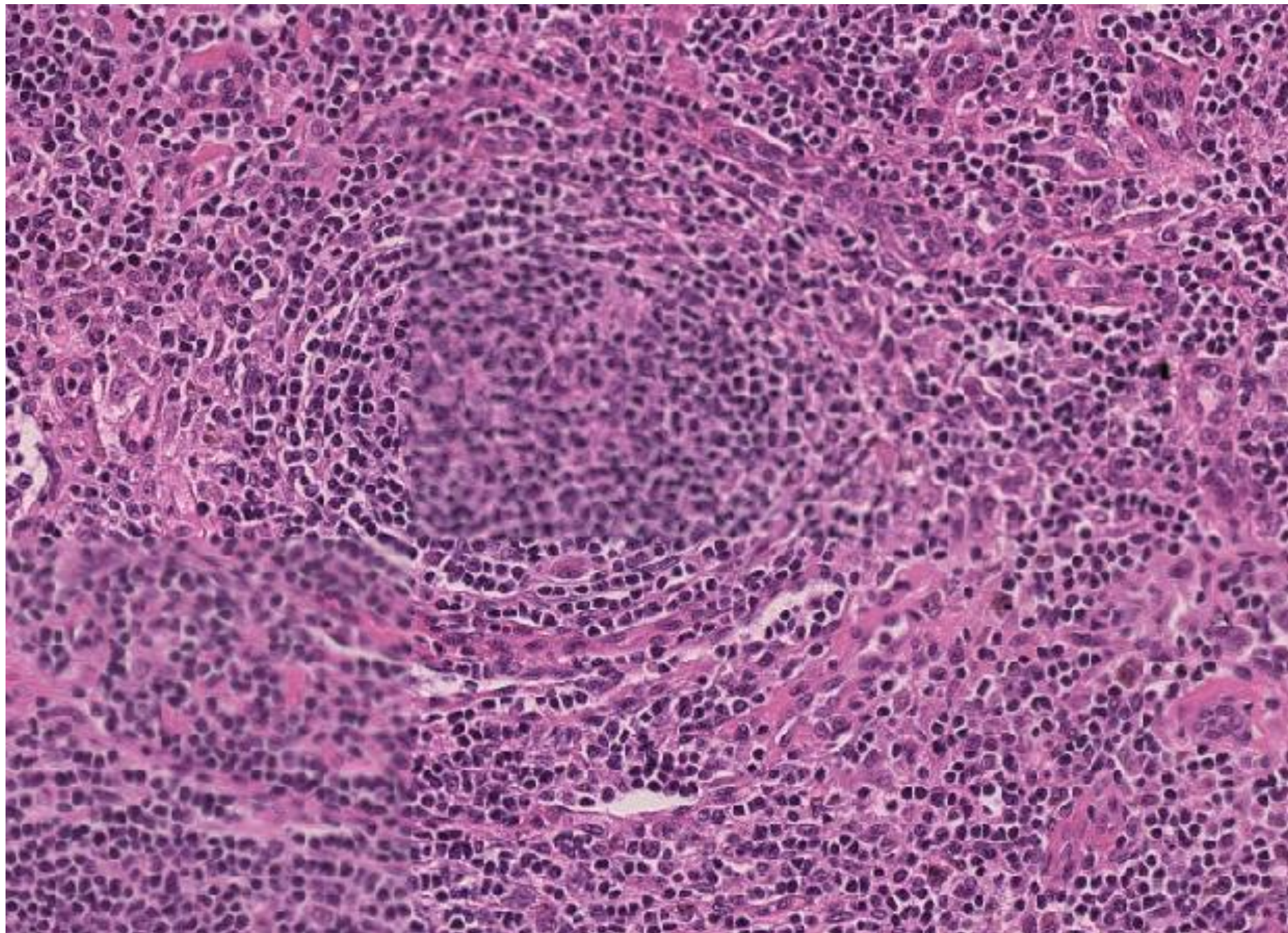
and **Bhaumik Shah, MD.**
Hematopathology Fellow
Fox Chase Cancer Center
Philadelphia, PA

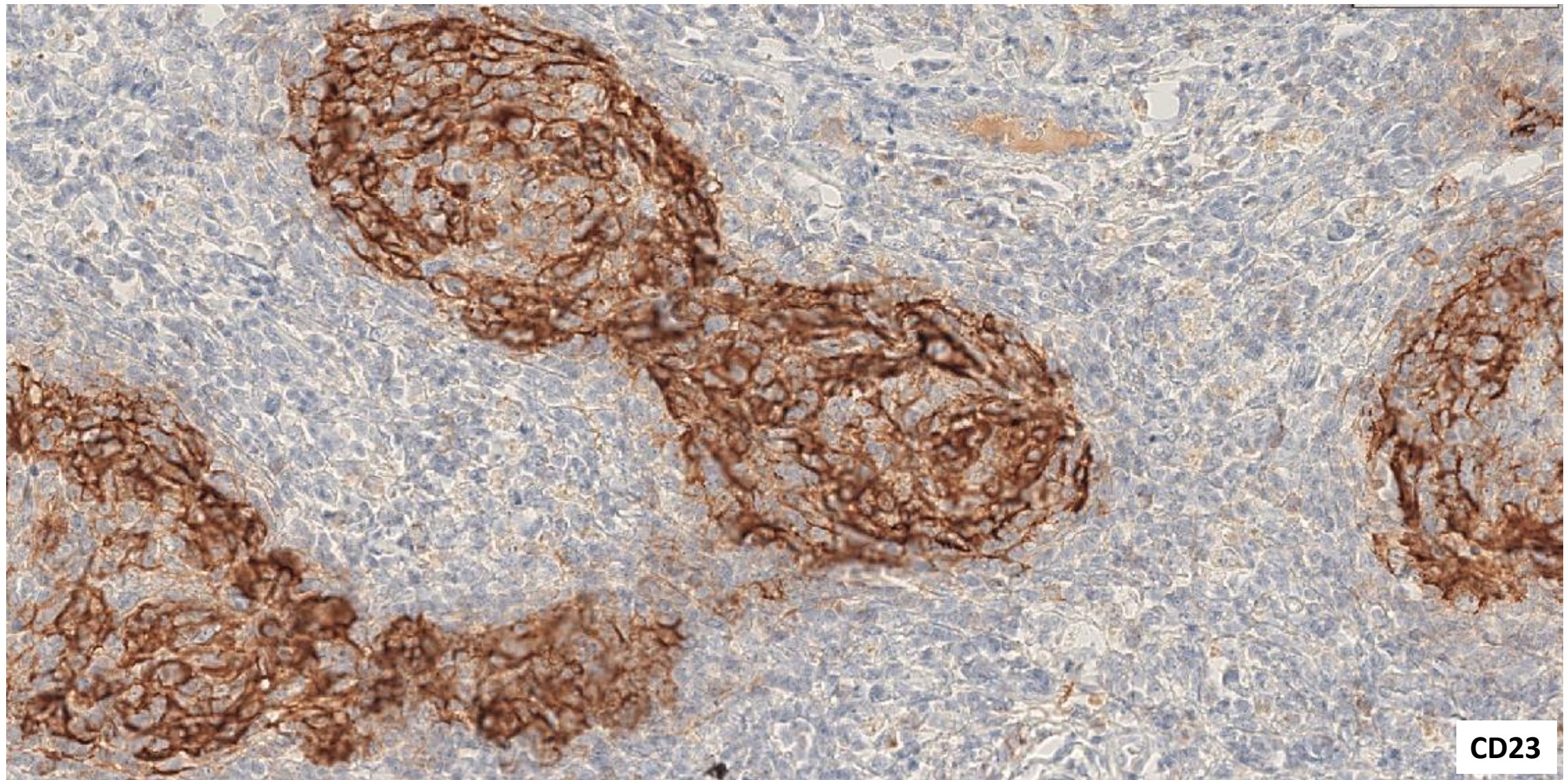
Case 2

- **81 years old female with PMH of A-fib & hypertension:**
- **Clinical:**
 - Presented with growing lump in her right groin, associated with profound fatigue and 25 lbs unintentional weight loss over last 12 months.
- **Labs:**
 - CBC, CMP, Coags, LDH, ANA, RF, CCP, TSH, SPEP/IFE/FLC/IgG/IgA/IgM unremarkable
 - **ESR 37, CRP 1.9 mg/dL, IL6 10.3 pg/mL (nml <5)**
- **PET Scan**
 - Bilateral iliac, pelvic and inguinal LAD (4.5 cm) with SUV max 13.75 in R iliac.
- **Procedure:**
 - Right inguinal lymph node excisional biopsy
 - With an outside institution diagnosis of **possible Castleman Disease.**

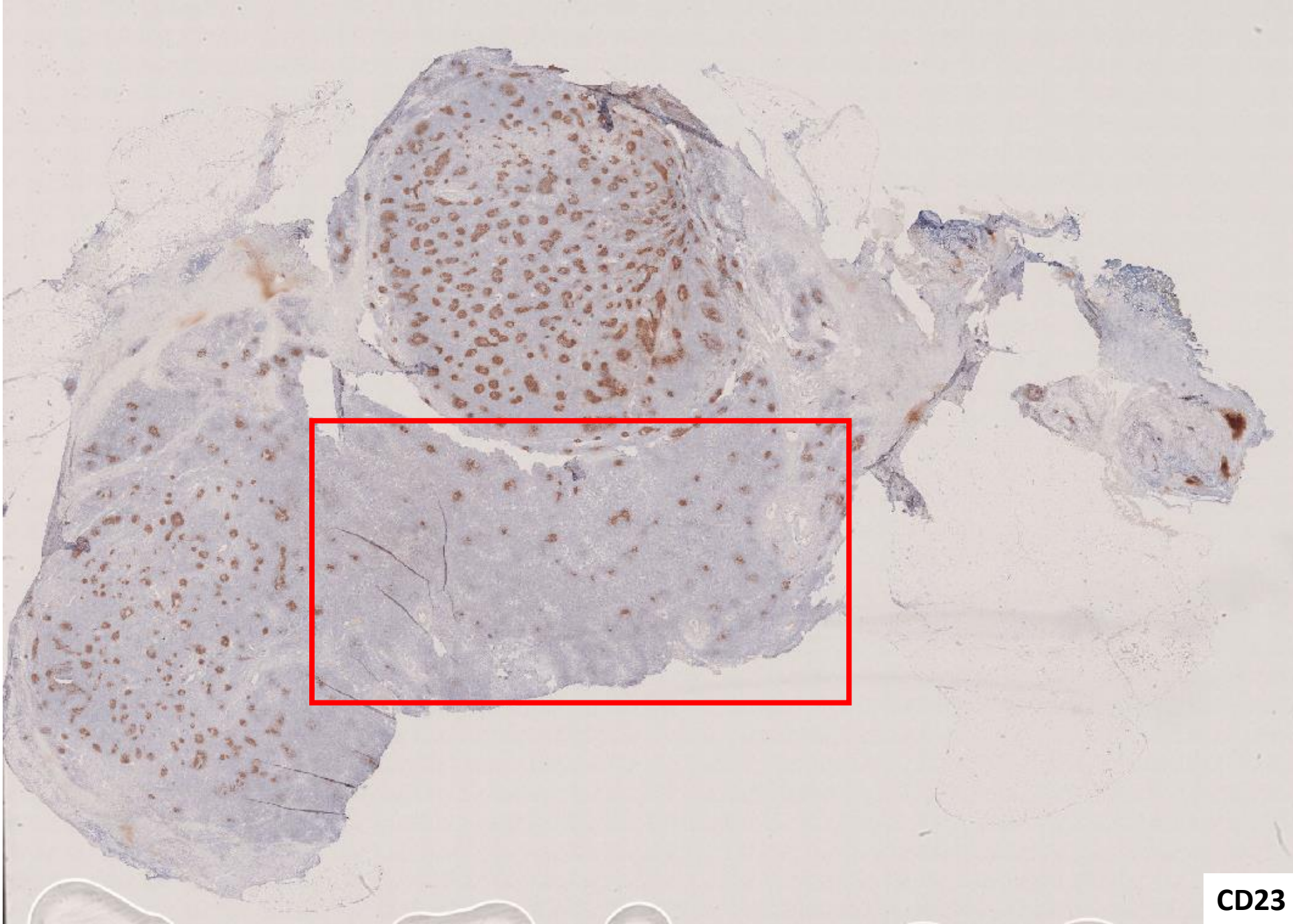




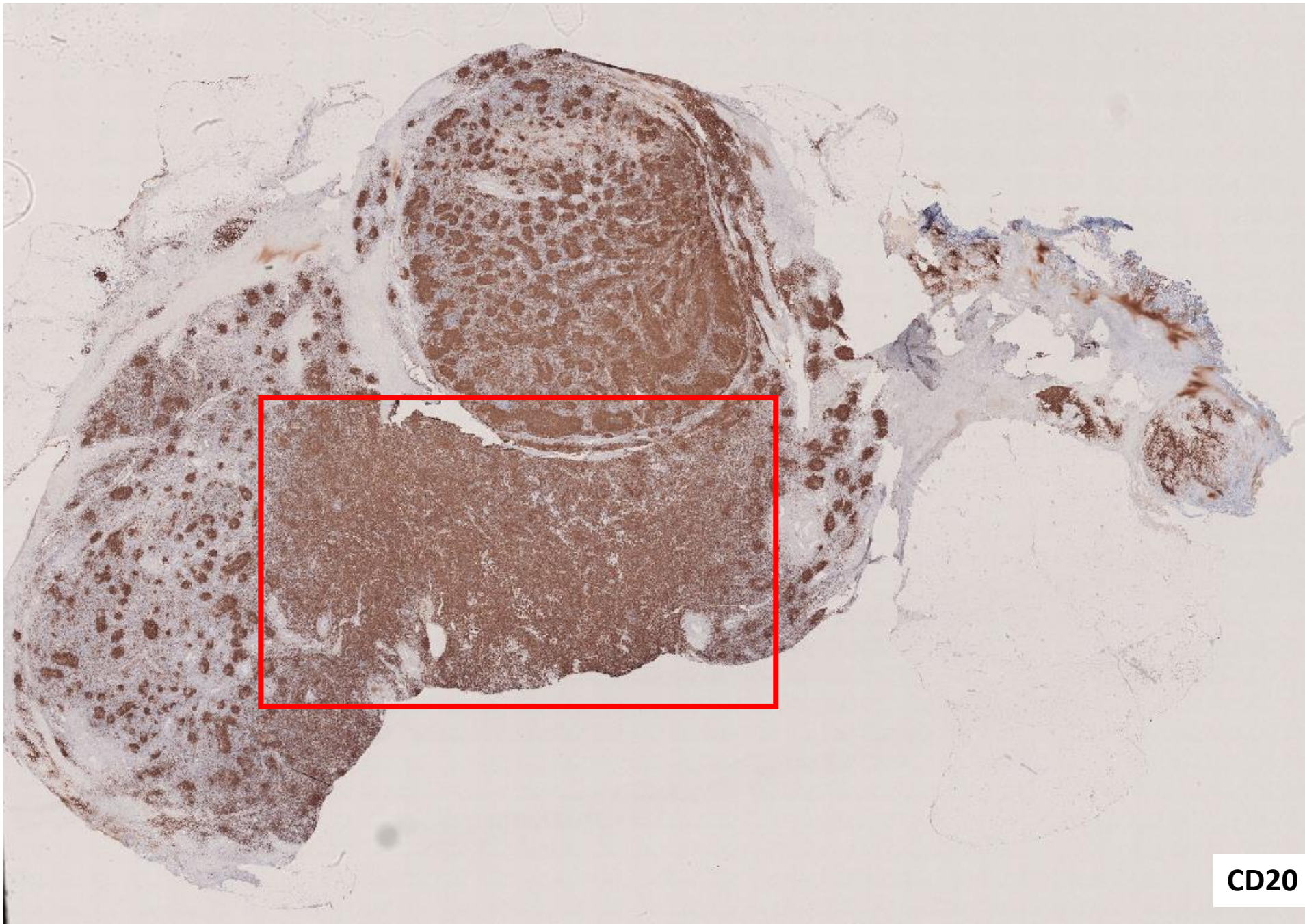




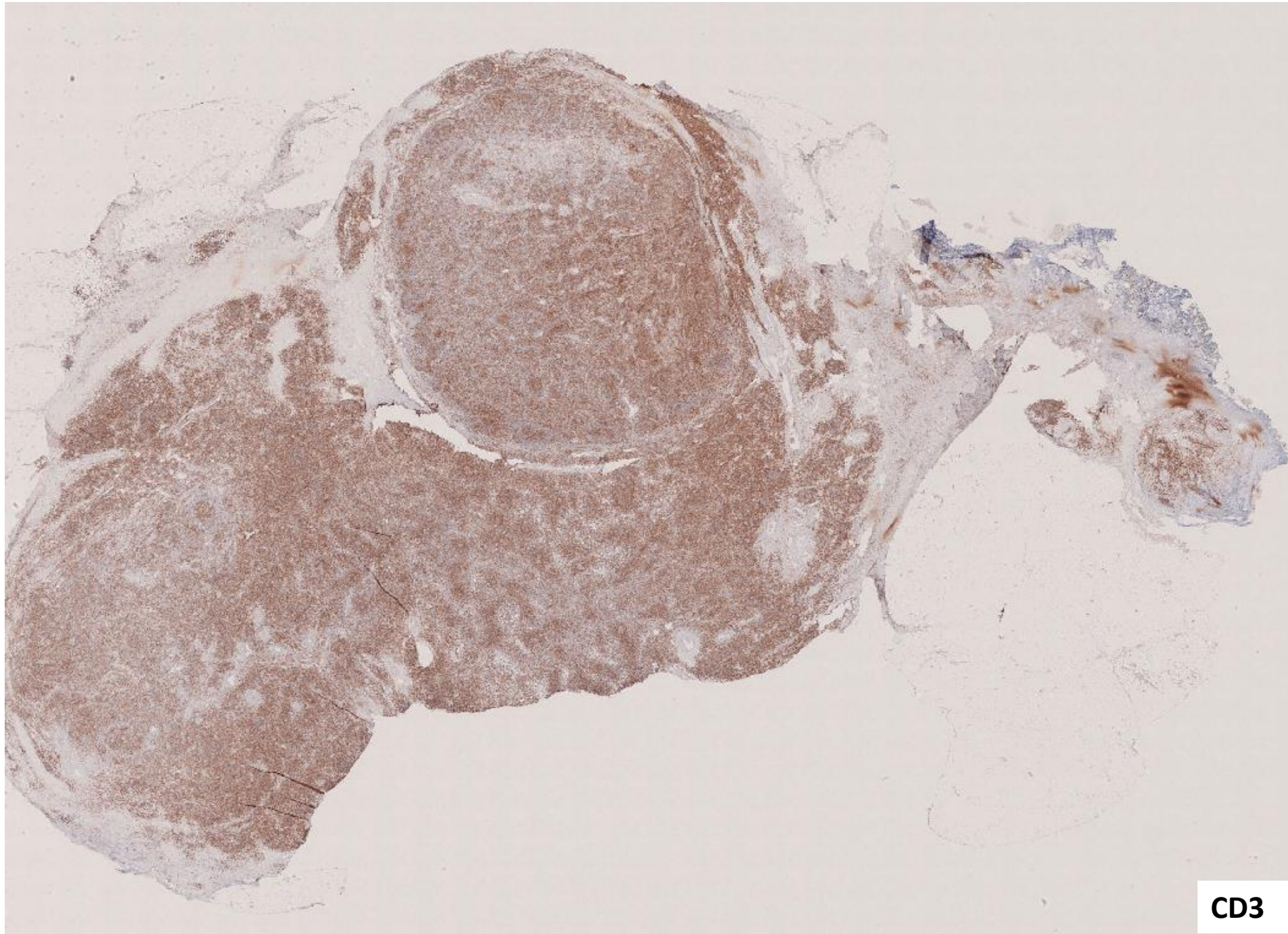
CD23



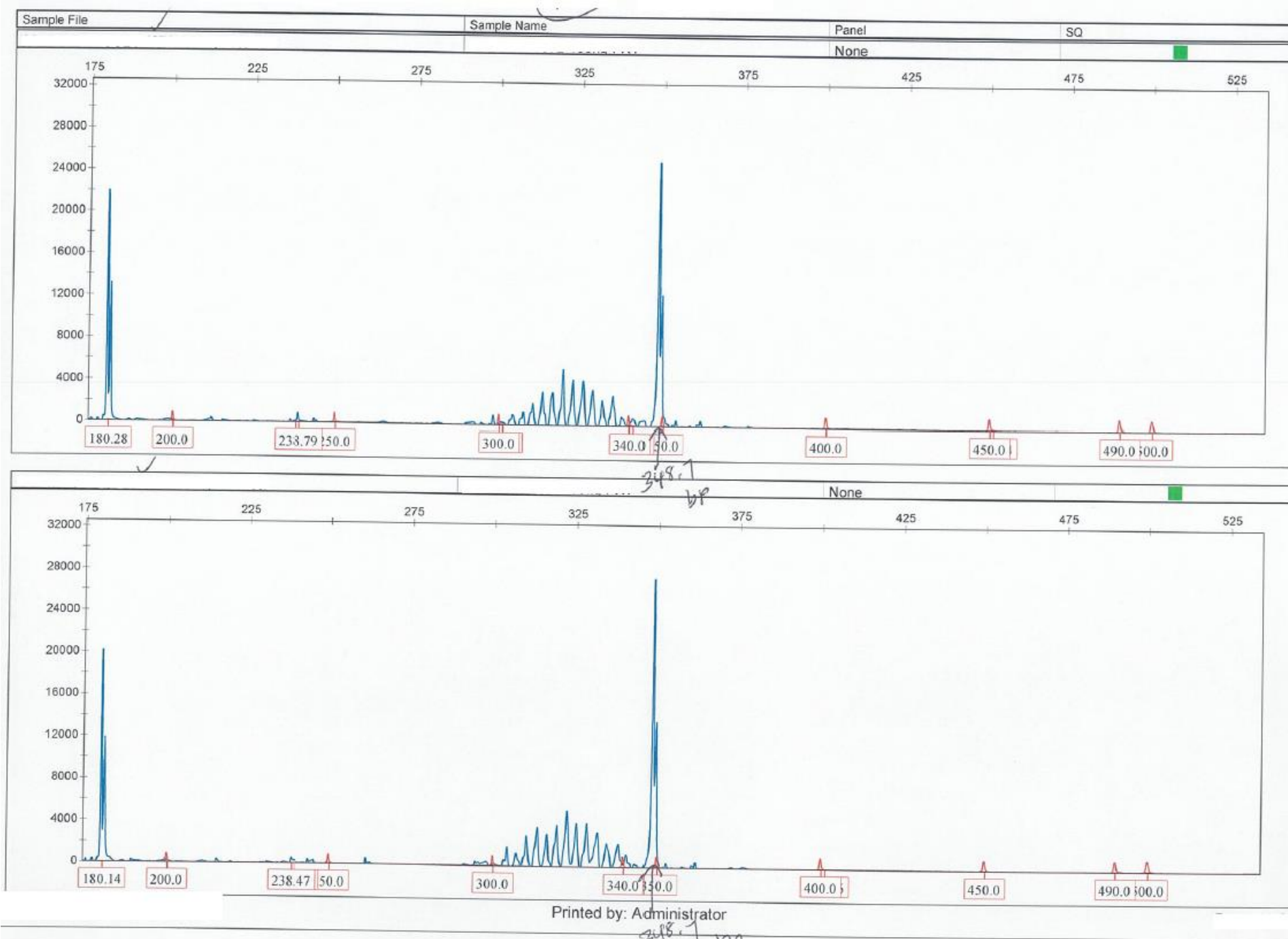
CD23



CD20



CD3



Clonal IGH gene rearrangement

Additional studies; Results

Immunohistochemistry	Large B-cells are CD20+, CD79a+, BCL6+ (40%, weak), BCL2+, MUM1+, CD10-, CD45+, CD15-, CD30-, CD138-, CyclinD1- and Ki67 (Focal 70%) Scattered T-cells CD3+, CD5+ Follicular dendritic cells: CD23+				
Chromosomal Micro Array	No abnormal findings				
FISH	Positive for gain of a MYC fusion signal and gain of a BCL6 fusion signal				
Clonal IGH gene rearrangement	Positive				
Next Generation Sequencing / Comprehensive Cancer Profile	Gene	Protein Change	cDNA Change	VAF	Tier
	BRAF	p.Lys601Glu	c.1801A>G	6.3%	Tier 2
	KMT2D	p.Trp1591*	c.4773G>A	6.3%	Tier 2
	EGFR	p.Pro228Arg	c.683C>G	49.3%	Tier 3

Case 2: Diagnosis

Diffuse large B-cell lymphoma with Castleman-like features.

OUTLINE

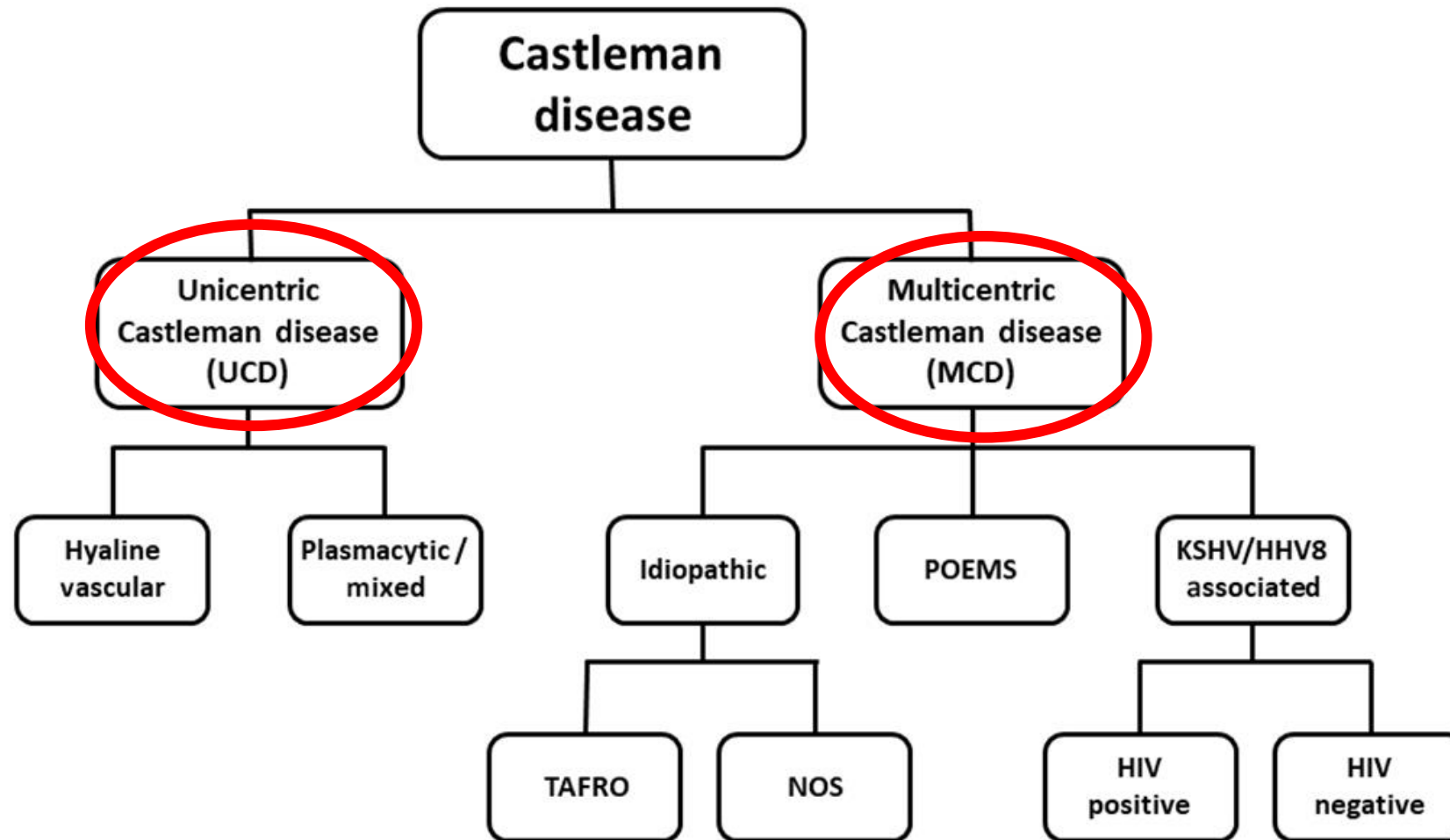
- Overview of Castleman Disease
- Lymphomas with Castleman-like changes.
- Literature review and case reports

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**

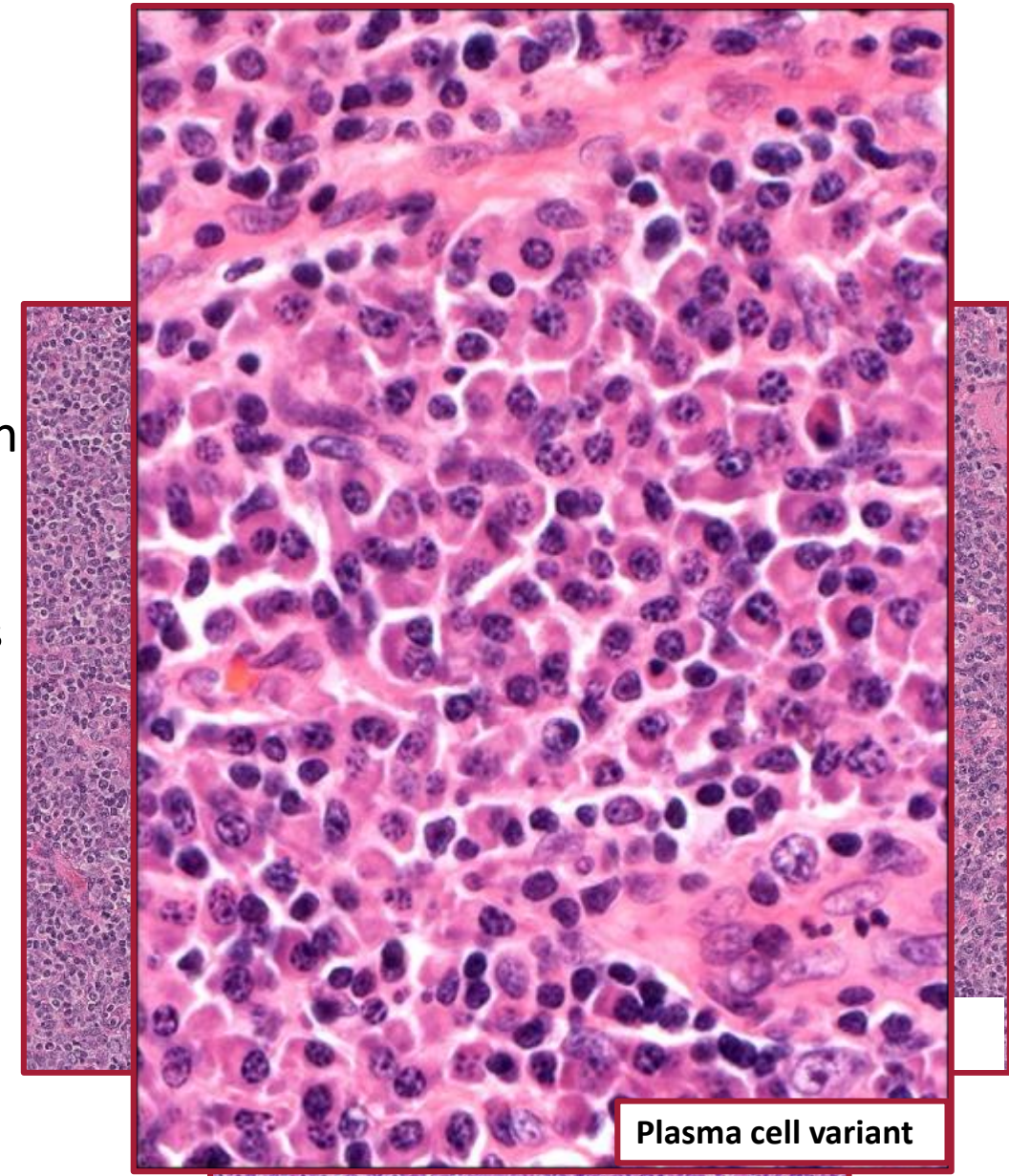
- **UCD:** Localized to a single lymph node station; often asymptomatic, discovered incidentally.
- **MCD:** Systemic symptoms (fever, weight loss, night sweats), generalized lymphadenopathy, possible organomegaly.
- **Association with HHV-8:** Particularly in immunocompromised (e.g., HIV).
- **IL-6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

Castleman Disease – Histopathology & Key Features

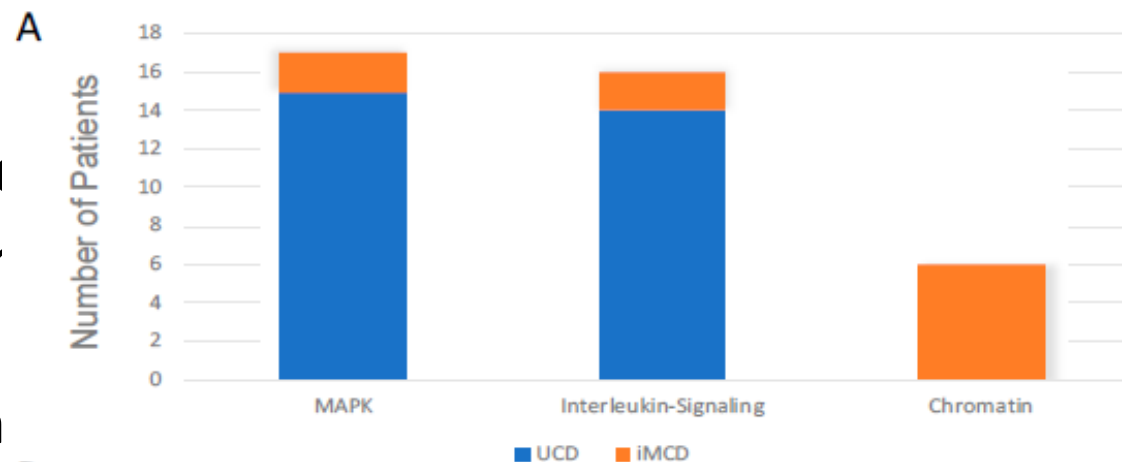
- Immunophenotype

- Immunostain

- HHV-8 testin

- Serum IL-6 ca

- Germline mu



B

Pathways	UCD	iMCD
MAPK pathway	<i>FAS, PDGFRB, FGFR3, NF1, IL6ST, HRAS, KRAS, NRAS, ERBB4, JAK3, BRAF and TGFR2</i>	<i>PTPRR, ERBB2, FAS, STK3, TGFR2</i>
Interleukin signaling pathway	<i>PDGFRB, FGFR3, NF1, PIM1, PTPN6, IL6ST, JAK1, HRAS, KRAS, NRAS, JAK2, AKT1, ERBB4, JAK3</i>	<i>ERBB2, JAK2, PTPN6</i>
Chromatin remodeling	none	<i>SETD1A, ASH1L, DOT1L, JAK2, KMT2E, DNMT3A</i>

licular areas.

V8.

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 Theodorides, 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

Case Reports in Hematology  **Forward Series**


BMJ Journals


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Human Pathology
Volume 68, October 2017, Pages 136-146






Human Pathology
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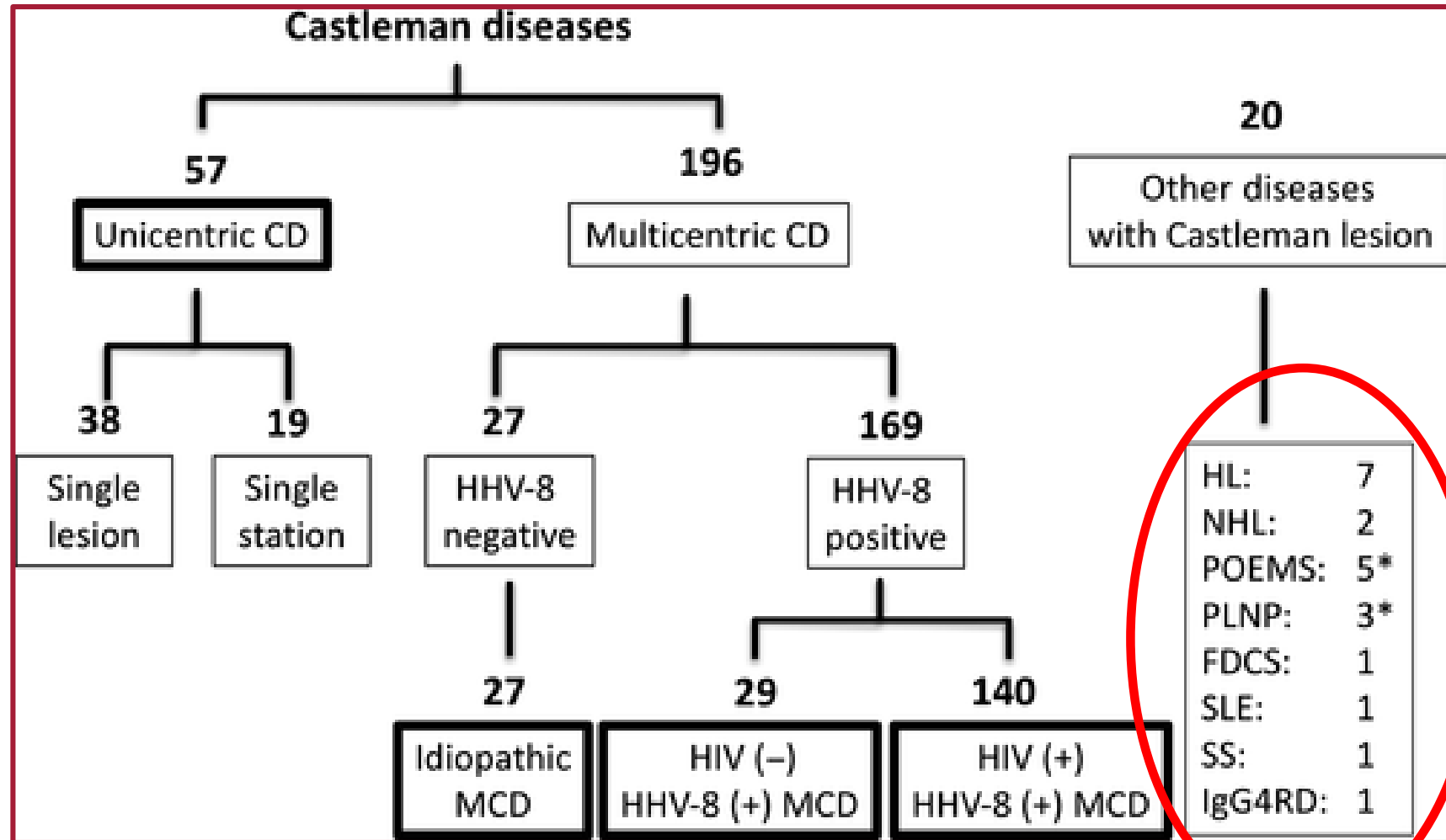
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**Angioimmunoblastic T-cell lymphoma:
Current Diagnostic Insights and Advances**

Sergio Pina
L. Jeffrey Me

Nana P. Matsumoto ^{a 1}  , Mina L. Xu ^b 

Castleman Like lymphomas literature review and case reports



Summary of case reports for Castleman Like lymphomas case reports

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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.

Angioimmunoblastic T-cell lymphoma: Current Diagnostic Insights and Advances. Matsumoto NP, Xu ML. Hum Pathol. 2024 Nov 19:105696. doi: 10.1016/j.humpath.2024.105696. Epub ahead of print. PMID: 39571692.

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.

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

And

Drs. Damsker and Stack for helping us
with the case presentation.



TEMPLE HEALTH

2/26/2025

