Immunohistochemistry in challenging hematology cases: old friends and new acquaintances

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Nothing to disclose

Learning objectives

- Demonstrate the utility of “traditional SurgPath” IHC markers in hematopathology practice.
- Discuss best practices in interpretation and reporting of some IHC stains.
- Review newer IHC stains in hematopathology.
- Underline diagnostic workup of morphologically challenging hematopathology cases.

PATIENT 1

Male in his 60's with right hemicolectomy and excision of inguinal lymph node

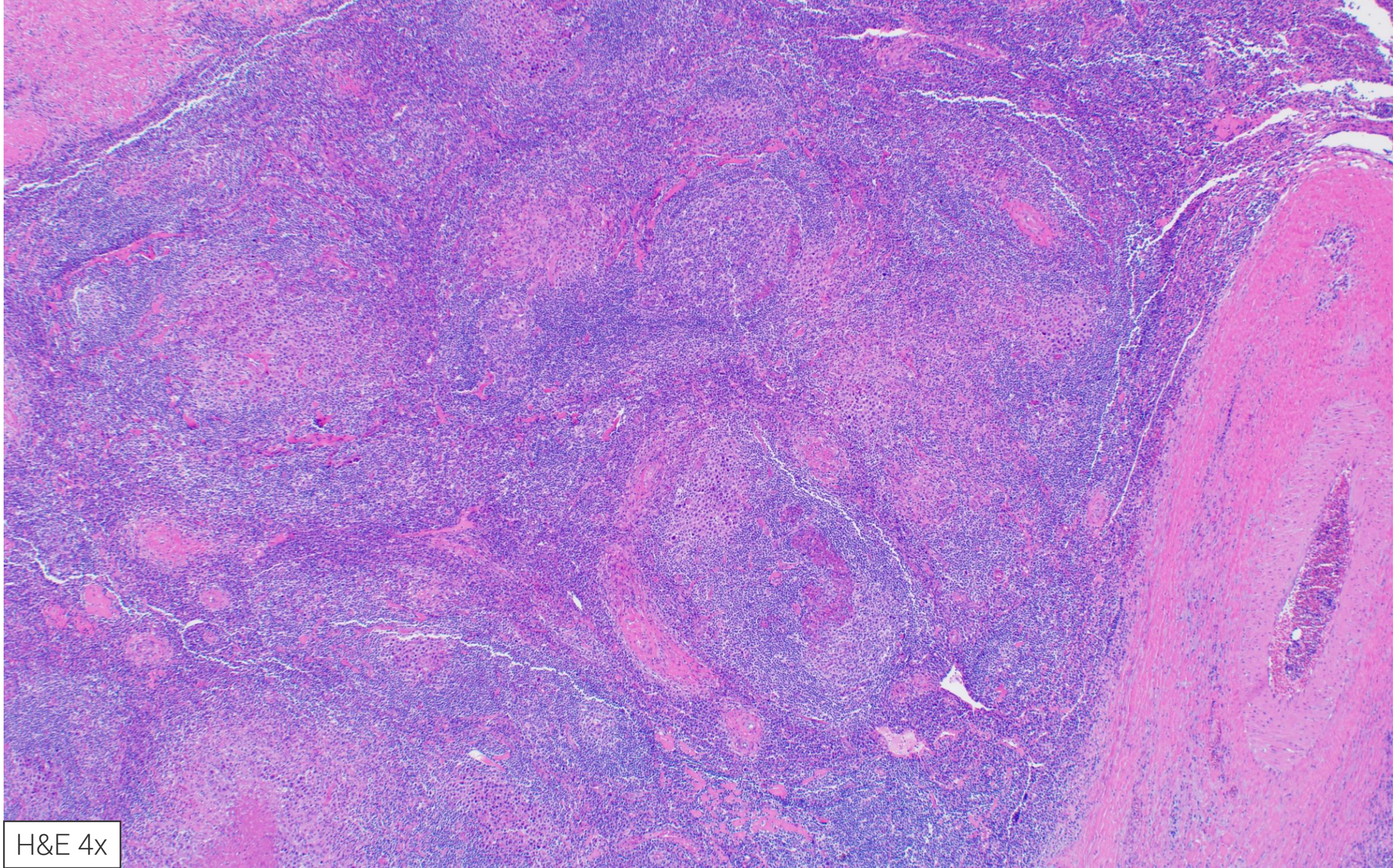
- Colon:

Mucinous adenocarcinoma with invasion into pericolic tissue and no mesenteric lymph node involvement (0/19); mismatch repair proteins are intact

- Left inguinal LN
  - » 6 x 4 x 3 cm with fleshy tan cut surface

Ancillary studies:

- Flow cytometry: polytypic B-cells and T-cells with retained antigens
- CD4:CD8 = 4.4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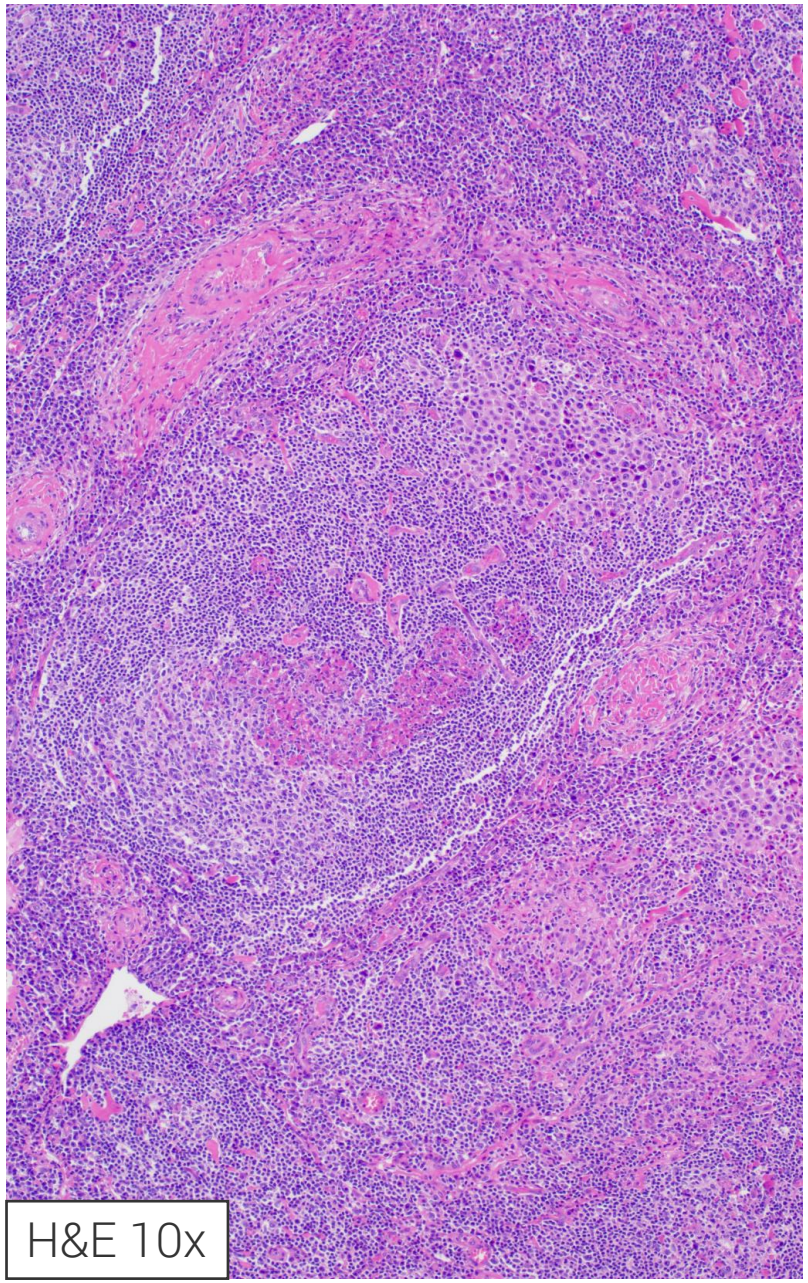

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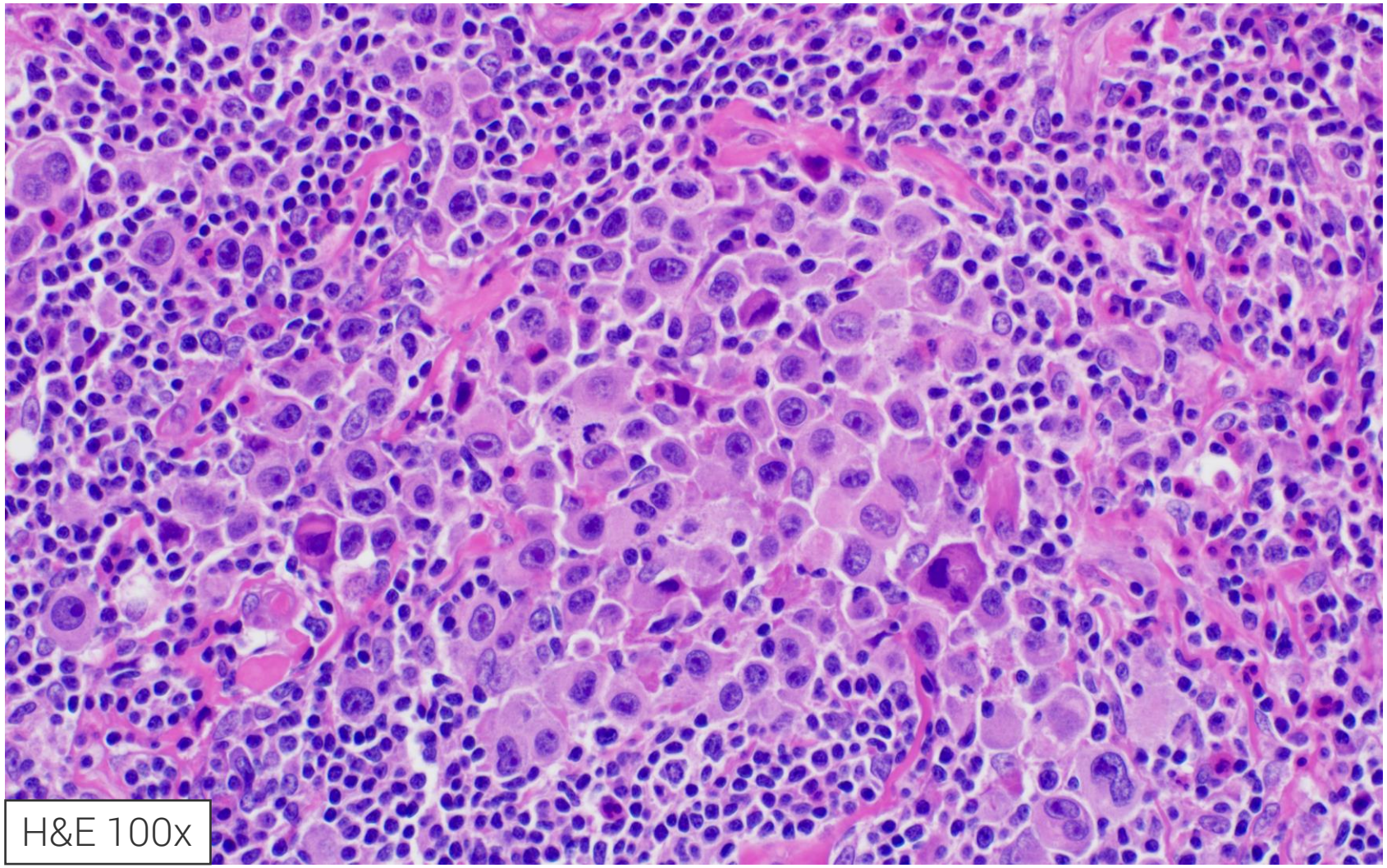

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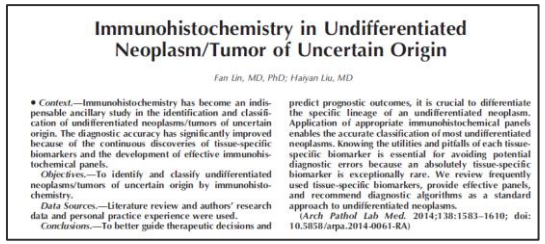


Immunohistochemistry in Undifferentiated Neoplasm/Tumor of Uncertain Origin

Fan Lin, MD, PhD; Haiyan Liu, MD

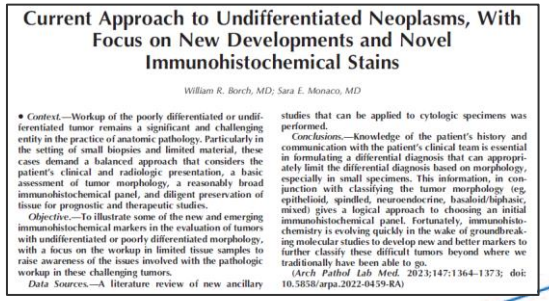
• *Context.*—Immunohistochemistry has become an indispensable ancillary study in the identification and classification of undifferentiated neoplasms/tumors of uncertain origin. The diagnostic accuracy has significantly improved because of the continuous discoveries of tissue-specific biomarkers and the development of effective immunohistochemical panels.

Objectives.—To identify and classify undifferentiated neoplasms/tumors of uncertain origin by immunohistochemistry.

Data Sources.—Literature review and authors' research data and personal practice experience were used.

Conclusions.—To better guide therapeutic decisions and predict prognostic outcomes, it is crucial to differentiate the specific lineage of an undifferentiated neoplasm. Application of appropriate immunohistochemical panels enables the accurate classification of most undifferentiated neoplasms. Knowing the utilities and pitfalls of each tissue-specific biomarker is essential for avoiding potential diagnostic errors because an absolutely tissue-specific biomarker is exceptionally rare. We review frequently used tissue-specific biomarkers, provide effective panels, and recommend diagnostic algorithms as a standard approach to undifferentiated neoplasms.

(*Arch Pathol Lab Med.* 2014;138:1583–1610; doi: 10.5858/arpa.2014-0061-RA)



Current Approach to Undifferentiated Neoplasms, With Focus on New Developments and Novel Immunohistochemical Stains

William R. Borch, MD; Sara E. Monaco, MD

• *Context.*—Workup of the poorly differentiated or undifferentiated tumor remains a significant and challenging entity in the practice of anatomic pathology. Particularly in the setting of small biopsies and limited material, these cases demand a balanced approach that considers the patient's clinical and radiologic presentation, a basic assessment of tumor morphology, a reasonably broad immunohistochemical panel, and diligent preservation of tissue for prognostic and therapeutic studies.

Objective.—To illustrate some of the new and emerging immunohistochemical markers in the evaluation of tumors with undifferentiated or poorly differentiated morphology, with a focus on the workup in limited tissue samples to raise awareness of the issues involved with the pathologic workup in these challenging tumors.

Data Sources.—A literature review of new ancillary studies that can be applied to cytologic specimens was performed.

Conclusions.—Knowledge of the patient's history and communication with the patient's clinical team is essential in formulating a differential diagnosis that can appropriately limit the differential diagnosis based on morphology, especially in small specimens. This information, in conjunction with classifying the tumor morphology (eg, epithelioid, spindled, neuroendocrine, basaloid/biphasic, mixed) gives a logical approach to choosing an initial immunohistochemical panel. Fortunately, immunohistochemistry is evolving quickly in the wake of groundbreaking molecular studies to develop new and better markers to further classify these difficult tumors beyond where we traditionally have been able to go.

(*Arch Pathol Lab Med.* 2023;147:1364–1373; doi: 10.5858/arpa.2022-0459-RA)

Undifferentiated or Poorly differentiated tumor

Clinicoradiological correlation to consider the statistically most probable sites of origin (consider age, biological sex, smoking status, prior history)

Assess morphology (at time of rapid on-site evaluation, frozen section or initial histology slides)

Epithelioid/Cohesive
Usually Vimentin-

Epithelioid/Discohesive
Usually Vimentin+

Spindled
Vimentin+

Mixed
Usually Vimentin+

p40, p63
SQUAMOUS/UROTHELIAL

CK
EPITHELIAL/ MESOTHELIAL

NE markers
NEUROENDOCRINE

S100, SOX10
NEUROGENIC/MELANOMA

CD45
LYMPHOID

SALL4, OCT3/4
GERM CELL

CKIT, DOG1
GIST

CD34, ERG, Actin
VASCULAR/SPINDLE CELL/OTHER

GATA3, Uroplakin, p16

CK7+/CK20-

CK7-/CK20+

CK7-/CK20-

Ki67, TTF1, POU2F3, CDX2, NKX3.1, GATA3, p16, ATRX, DAXX

MelanA, HMB45, MiTF, Tyrosinase

Lymphoma Workup CD20, CD3, CD30, PAX5, MUM1

CD30, CKIT, AFP, Glypican

Ki67, Desmin, MyoD1, STAT6

TTF1, GATA3, TRPS1, Calretinin, WT1, PAX8, SMAD4, Alb ISH, CDX2, CDH17

CDX2, SATB2, MCPyV

NKX3.1, Glypican, Arginase-1, SF-1, PAX8, Alb ISH

If non-specific immunophenotype or desire to stop IHC workup for molecular/biomarker studies, render morphology-based diagnosis with differential diagnosis

(Malignant) Epithelioid or Round Blue Cell Neoplasm

(Malignant) Spindle Cell Neoplasm

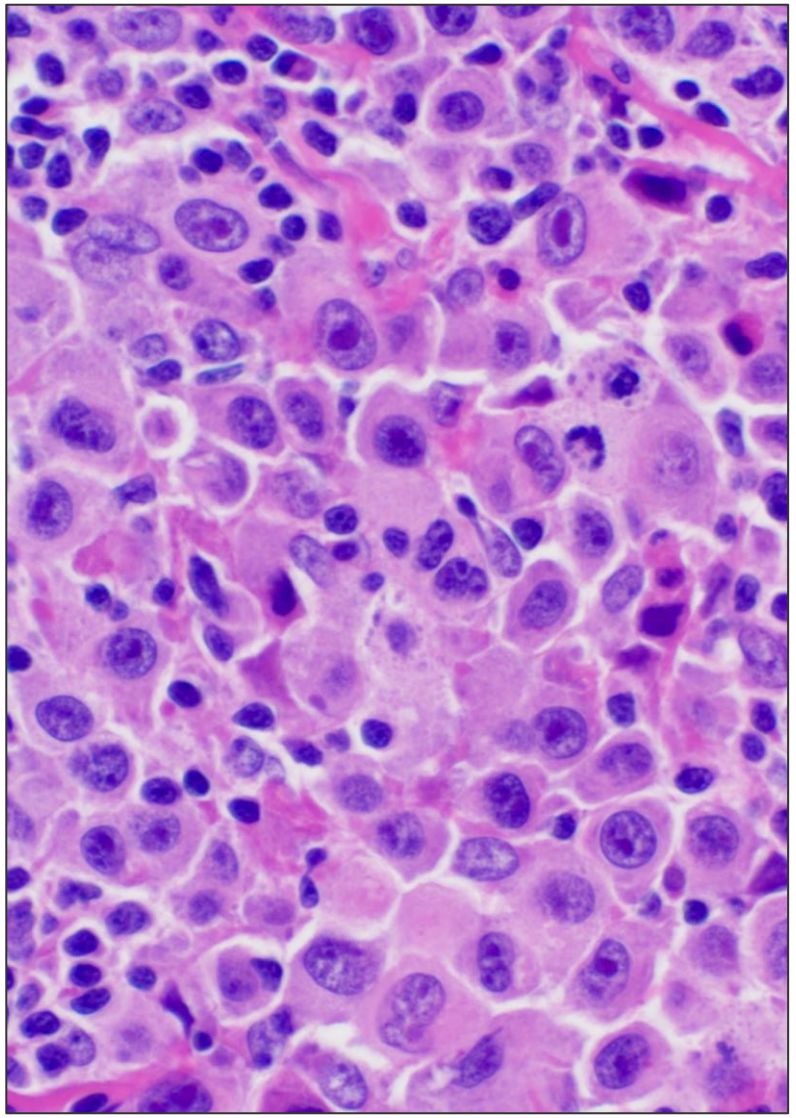
(Malignant) Epithelioid & Spindle Cell Neoplasm

Review of all additional biomarker testing and clinicoradiological findings to reach consensus (diagnostic management team, tumor board)

Borch WR, Monaco SE. Current Approach to Undifferentiated Neoplasms, With Focus on New Developments and Novel Immunohistochemical Stains. Arch Pathol Lab Med. 2023 Dec 1;147(12):1364-1373.

- Differential diagnosis

1) Carcinoma
2) Melanoma
3) Germ cell tumor
4) Lymphoma



- IHCs – round 1

AE1/AE3: negative

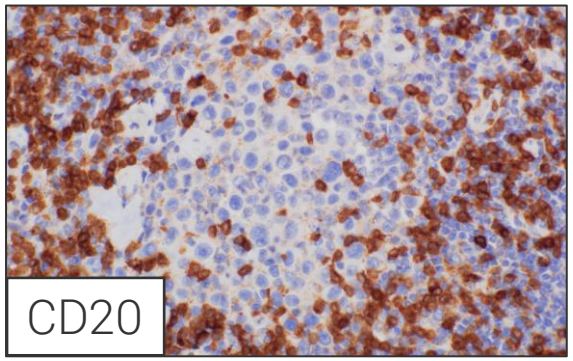
SALL4: negative

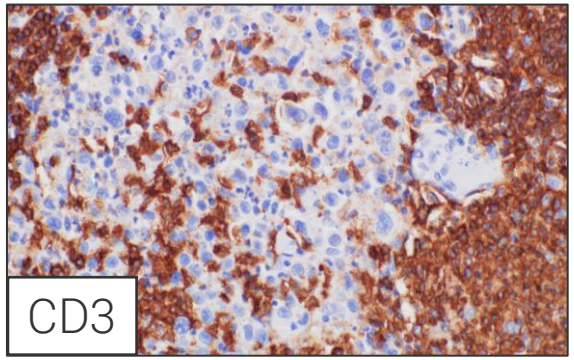
S100: negative

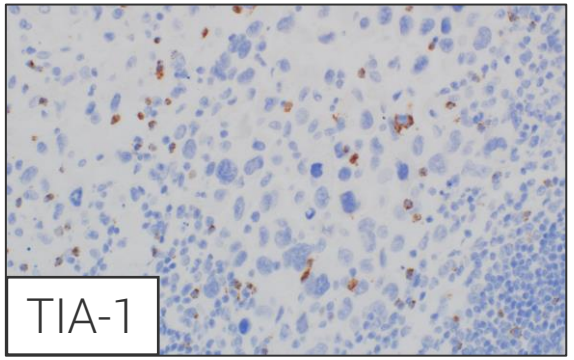
CD45: negative

Hemepath workup

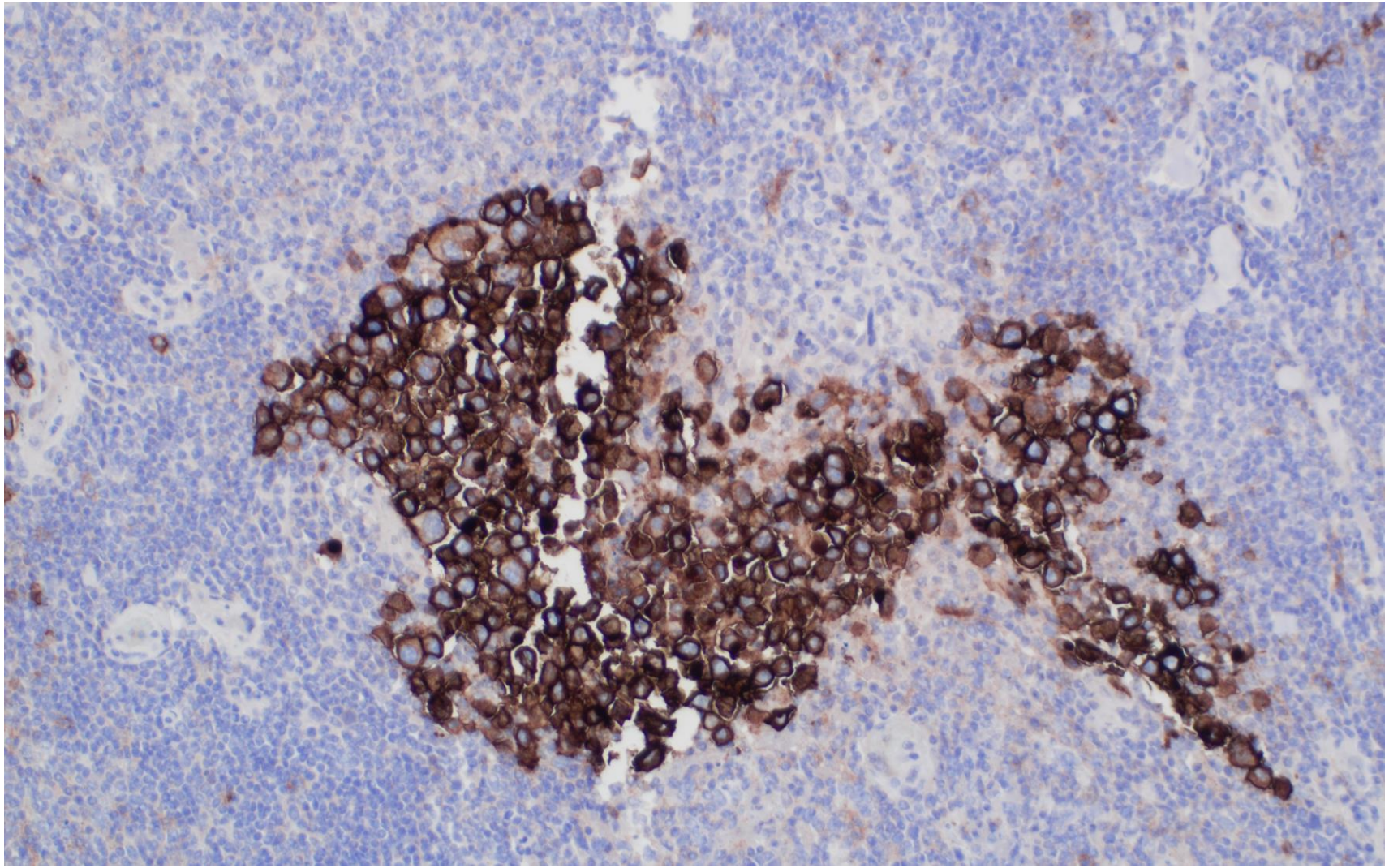
B-cell markers	T-cell markers	Other markers
• CD20 • CD19 • CD79a • PAX5	• CD3 • CD2, CD5 • CD4, CD8 • TIA1	• Myeloid: MPO, CD117 • Plasma cells/plasmablasts: CD138 • Histiocytes: CD68, CD163 • Viral infections: EBV, HHV8
NEGATIVE	NEGATIVE	NEGATIVE


CD20


CD3


TIA-1

Breakthrough: CD30



CD30

- Precursor CD30 protein transits through Golgi complex
- Mature CD30 is membranous
- Viral infection may induce CD30 activation in B- and T-cells
- Activated in some autoimmune diseases (RA)

- Therapy target: brentuximab

- Infections: EBV, CMV
- Lymphomas:

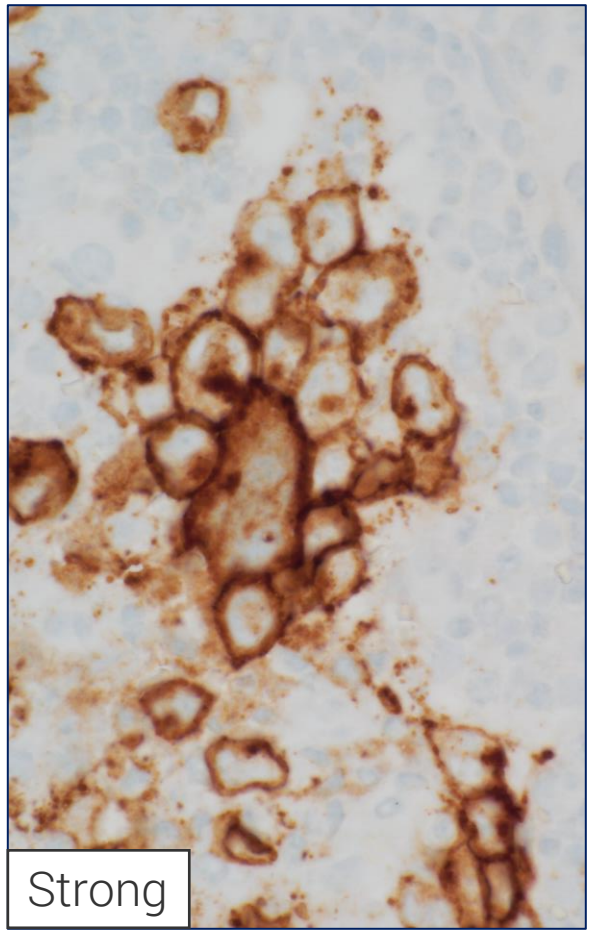
  B-cell: **CHL**, PMLBCL, some DLBCLs

  T-cell: **ALCL**, some cutaneous and other T-cell lymphomas

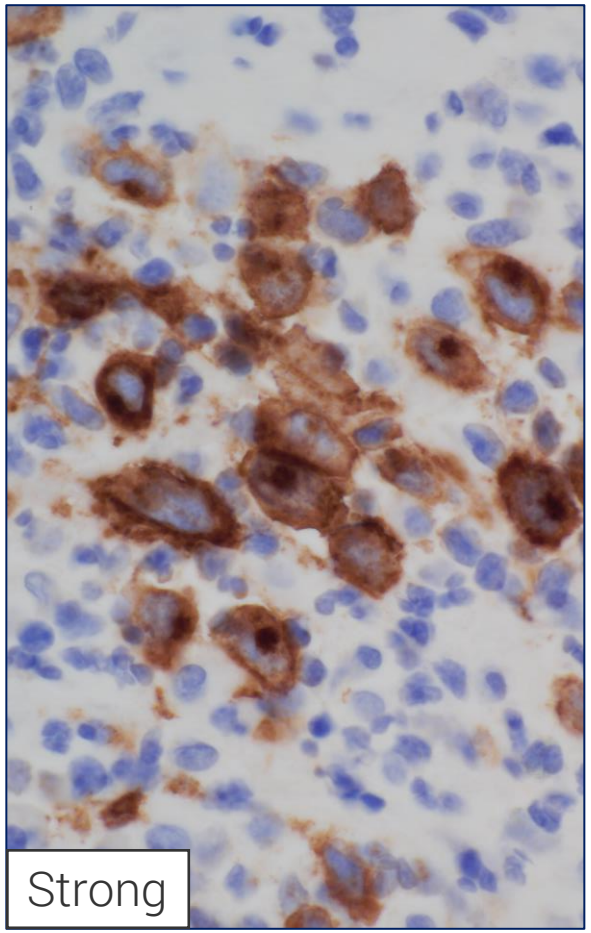
  EBV-associated lymphomas
- Systemic mastocytosis
- **Embryonal carcinoma**
- Melanoma
- Epithelioid myofibroblastic sarcoma

CD30 staining pattern

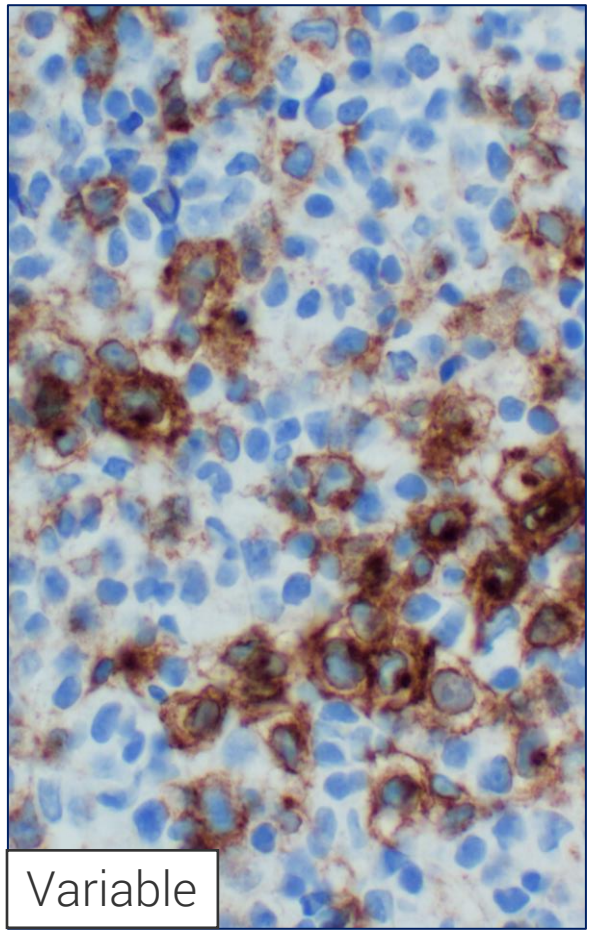
ALCL



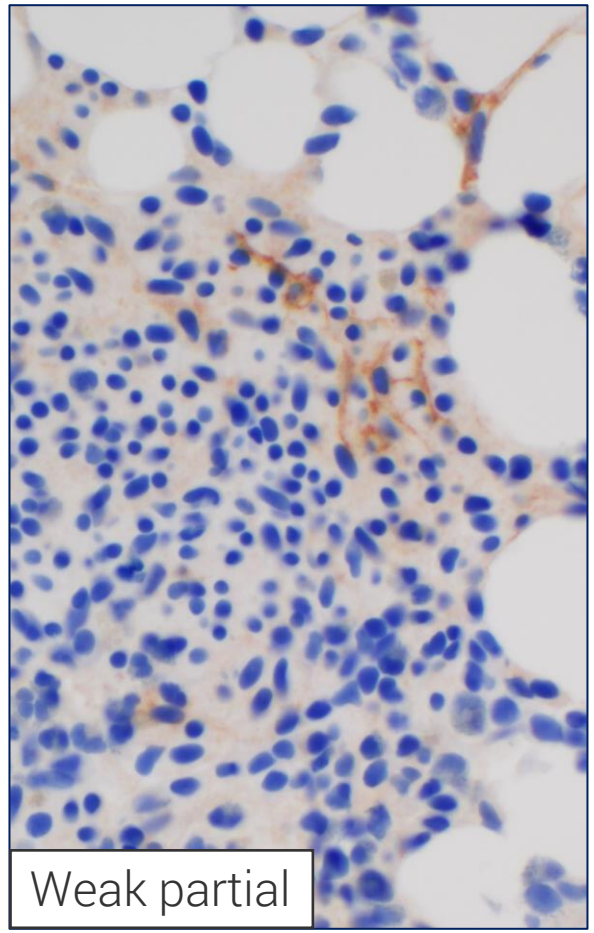
Classic Hodgkin lymphoma



EBV tonsilitis

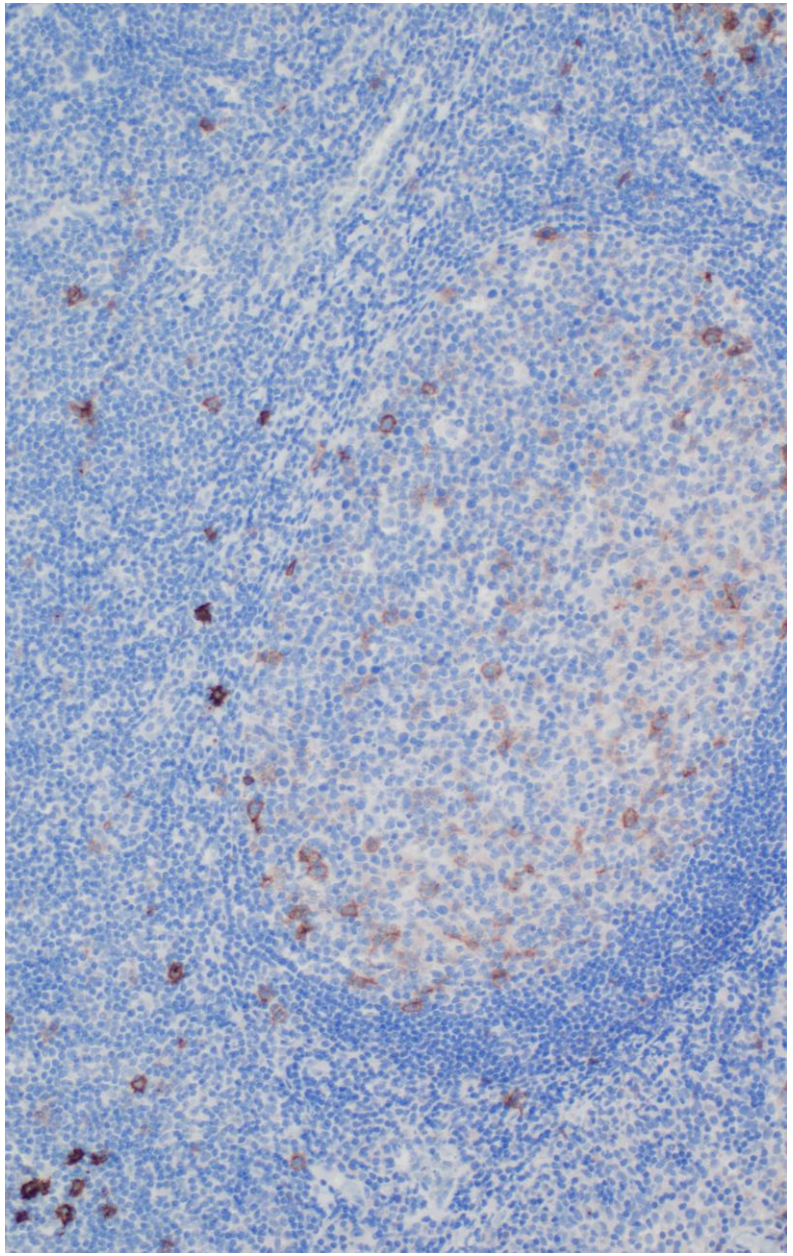


Systemic mastocytosis



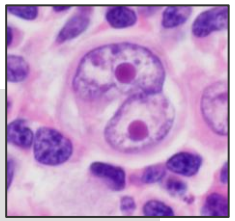
IHC positive tissue controls

- Performance of the primary antibody
- Ideally placed on the same slide as the patient's tissue
- Fresh surgical/biopsy specimen fixed and processed as soon as possible in the same manner as patient's sample
- Autopsy material is the last resort
- Tissue with well-characterized and reliable expression
- Low level expression – targeting the sensitivity of the assay



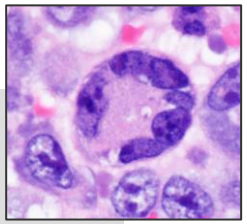
CHL vs ALCL

Classic Hodgkin lymphoma

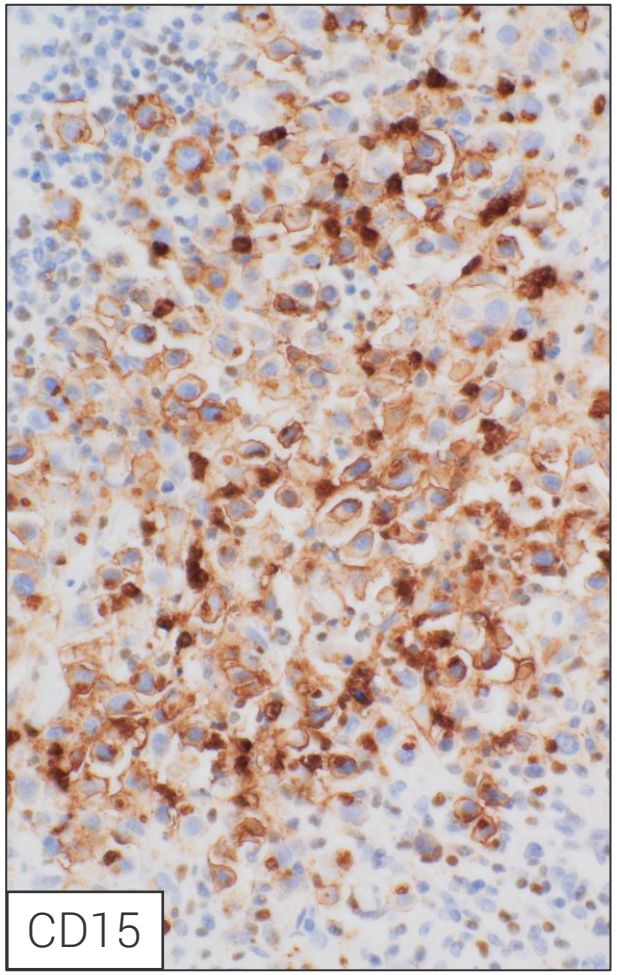


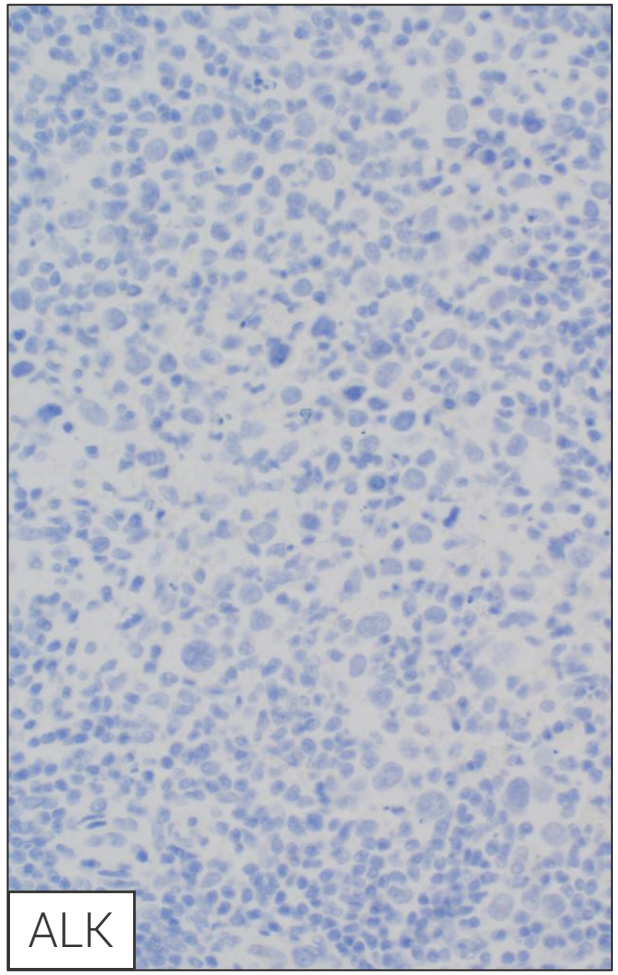
- Hodgkin cells and Reed-Sternberg cells
- Neoplastic cells are B-cell with abnormal B-differentiation program
  - » PAX5$^{95\%}$, CD19$^{5\text{-}10\%}$, CD20$^{15\%}$, CD22$^{5\text{-}10\%}$, CD79a$^{5\text{-}10\%}$, OCT2$^{5\text{-}10\%}$, BOB.1$^{5\text{-}10\%}$, MUM1$^{90\%}$
  - » Caveat: CD3+ and/or CD5+ (5% cases, mostly nodular sclerosis)
- Appropriate background

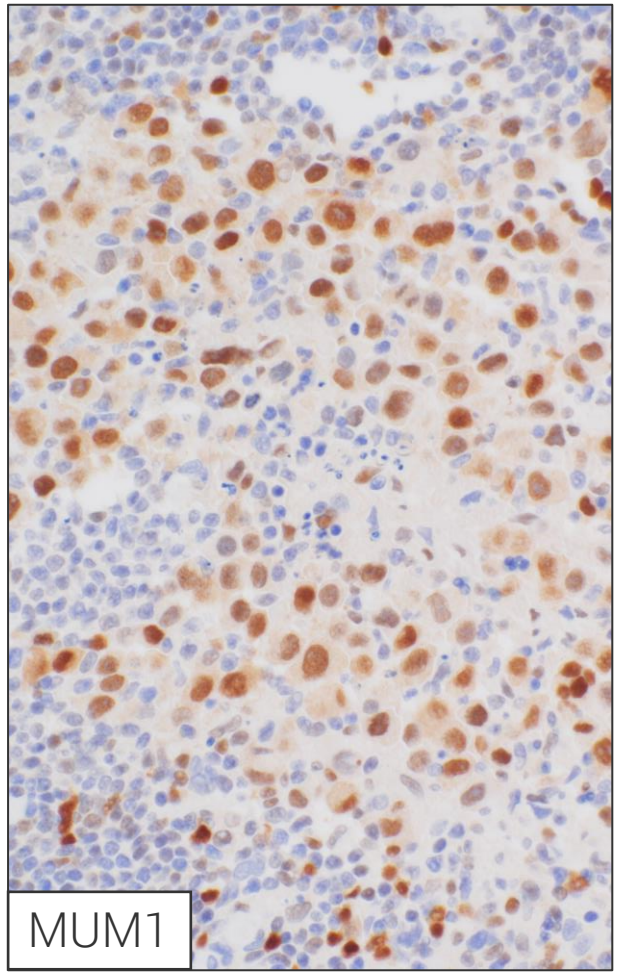
Anaplastic large cell lymphoma

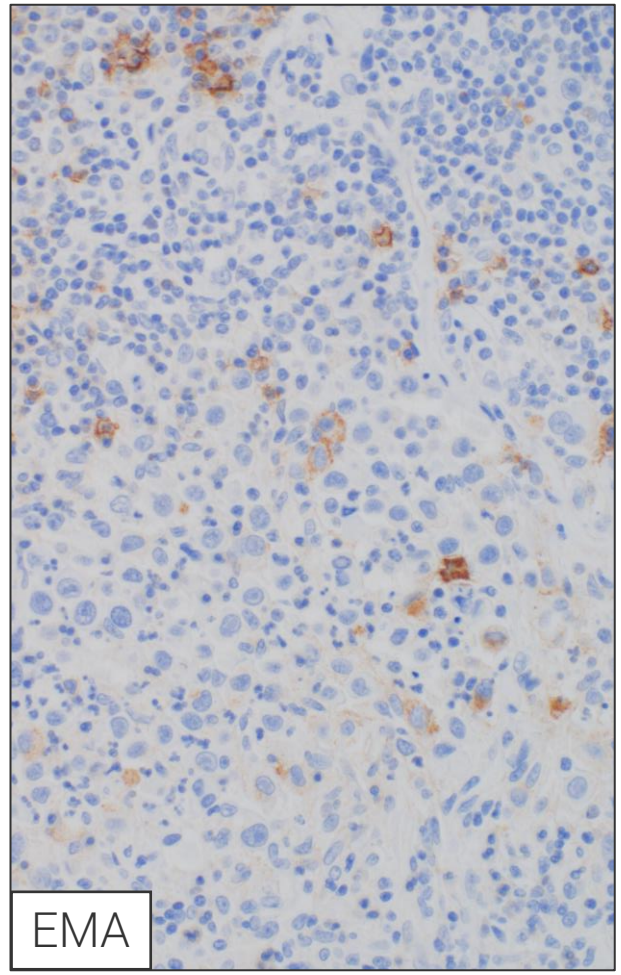


- Hallmark cells
- Neoplastic cells are T-cells
  - » CD2$^{+/-}$, CD3$^{\text{often }-}$, CD4$^{\text{mostly }+}$, CD8$^{\text{usually }-}$, CD5$^{\text{often }-}$, cytotoxic markers$^{\text{often }+}$, PAX5$^{-/\text{rarely}+}$
  - » ALCL panel should include CD4, TIA/Granzyme B
  - » ALK: positive in ALK+ ALCLs
  - » Caveat: CD15 can rarely be +
- Sinusoidal pattern



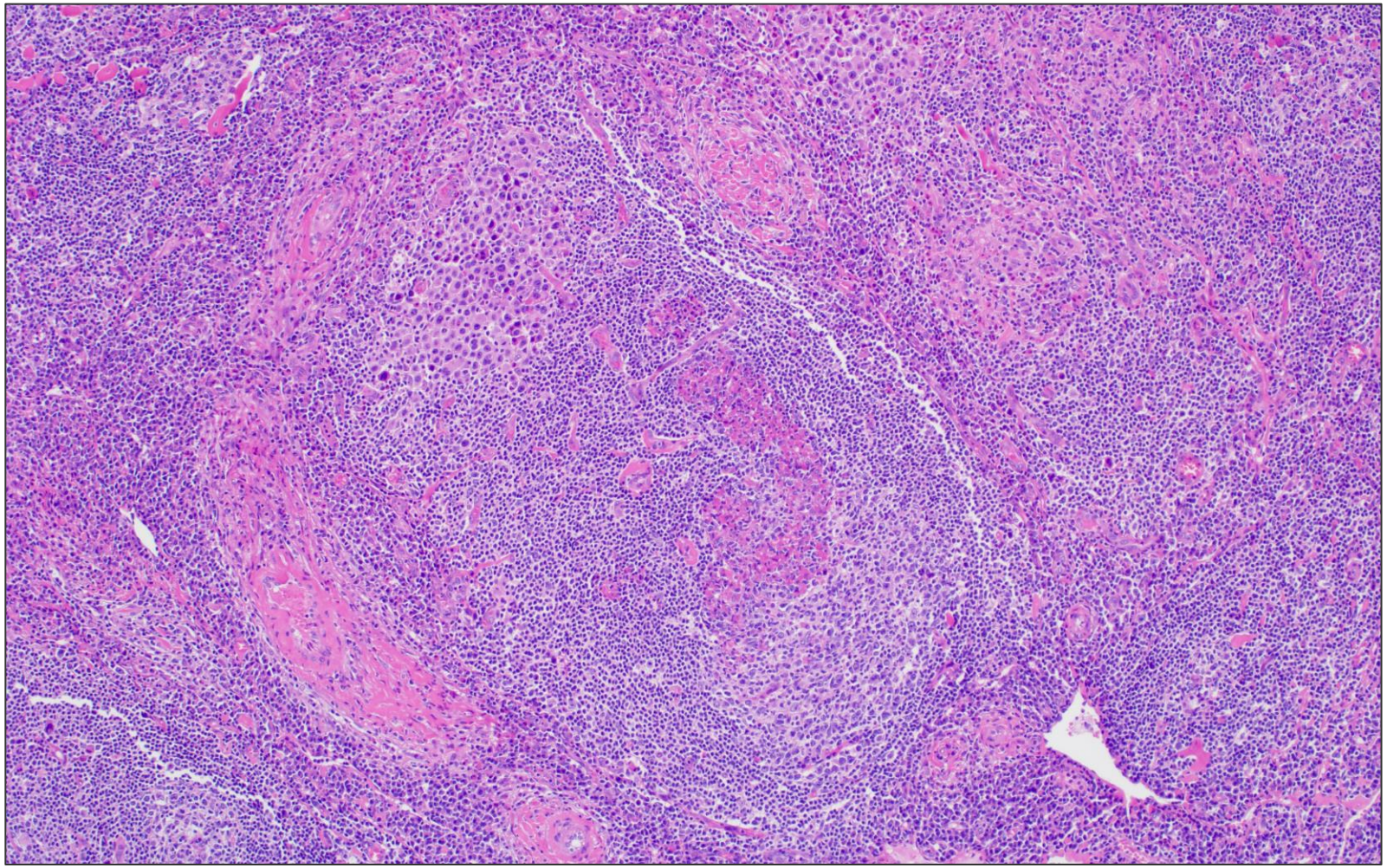




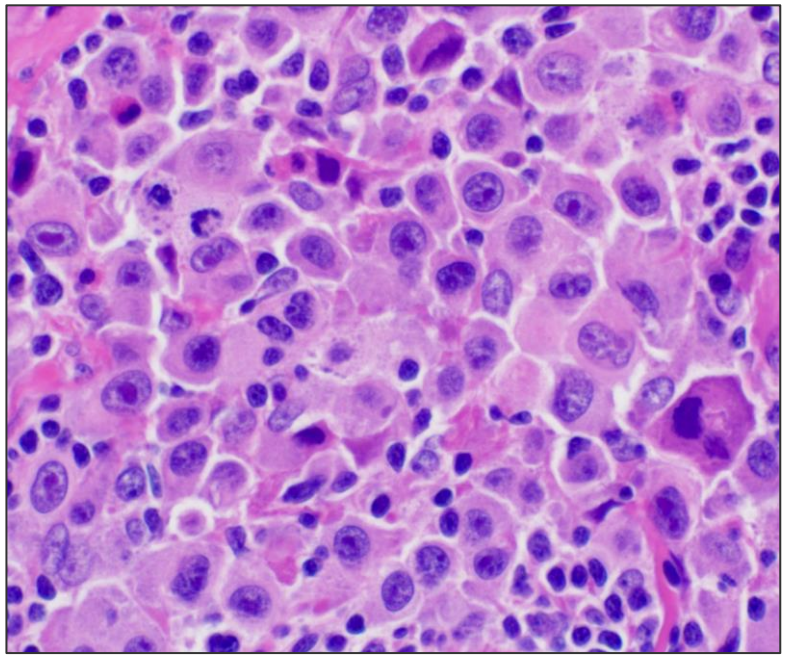


ALK-negative ALCL: Differential Dx

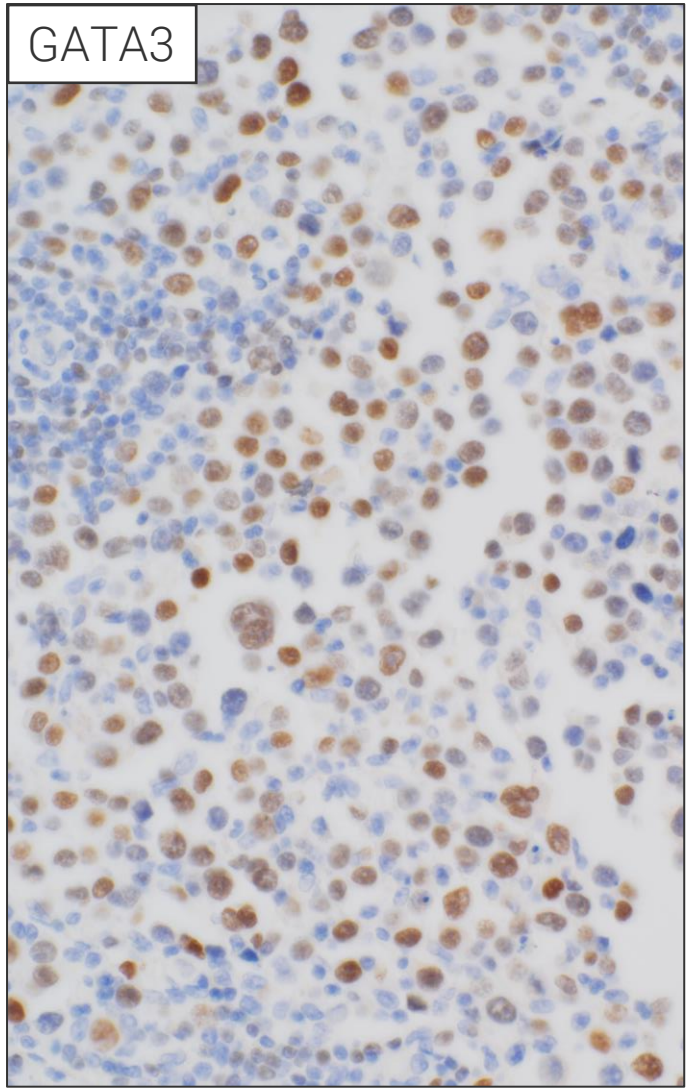
	ALCL, ALK-	PTCL, NOS	Anaplastic LBCL
Cytomorphology	Hallmark cells, pleomorphic cells	No hallmark cells, variable pleomorphism	Similar to ALCL
Distribution	Sinusoidal, “carcinoma-like”	Lacks ALCL distribution	Similar to ALCL
CD30	Strong	Variable, <75% cells	Can be +
T-cell markers	Variable, “null-type”	Variable	Negative
B-cell markers	PAX5, rarely	Negative	Positive
EMA	Variable	Negative	Negative
MUM1	Rarely	Variable	Variable



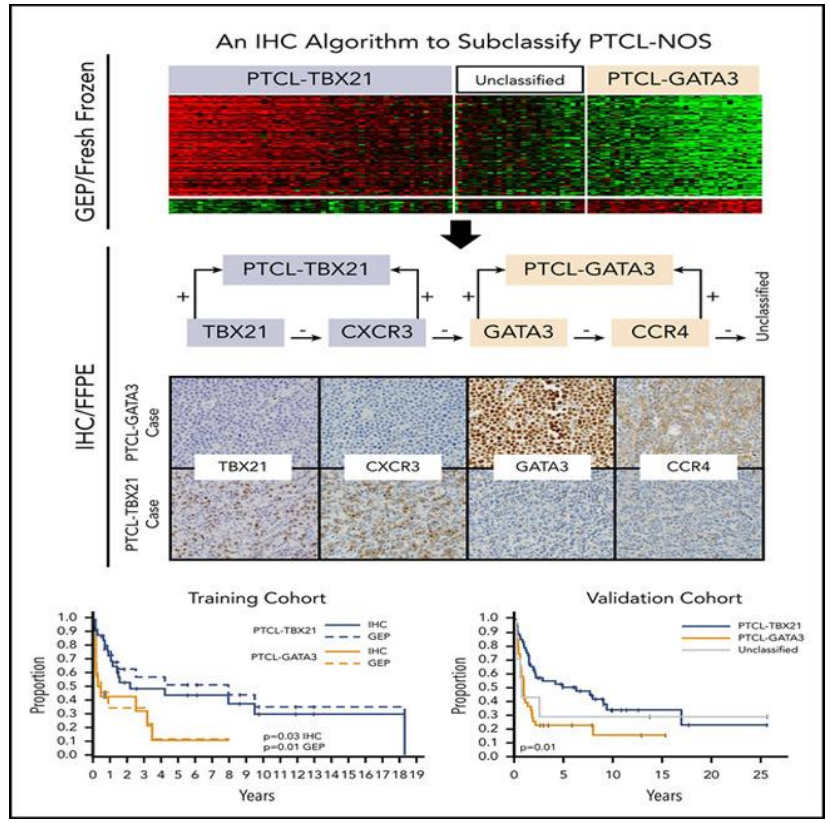
- Paracortical distribution, neoplastic cells surround germinal centers
- Occasional “hallmark cells”
- Neutrophils and eosinophils in background



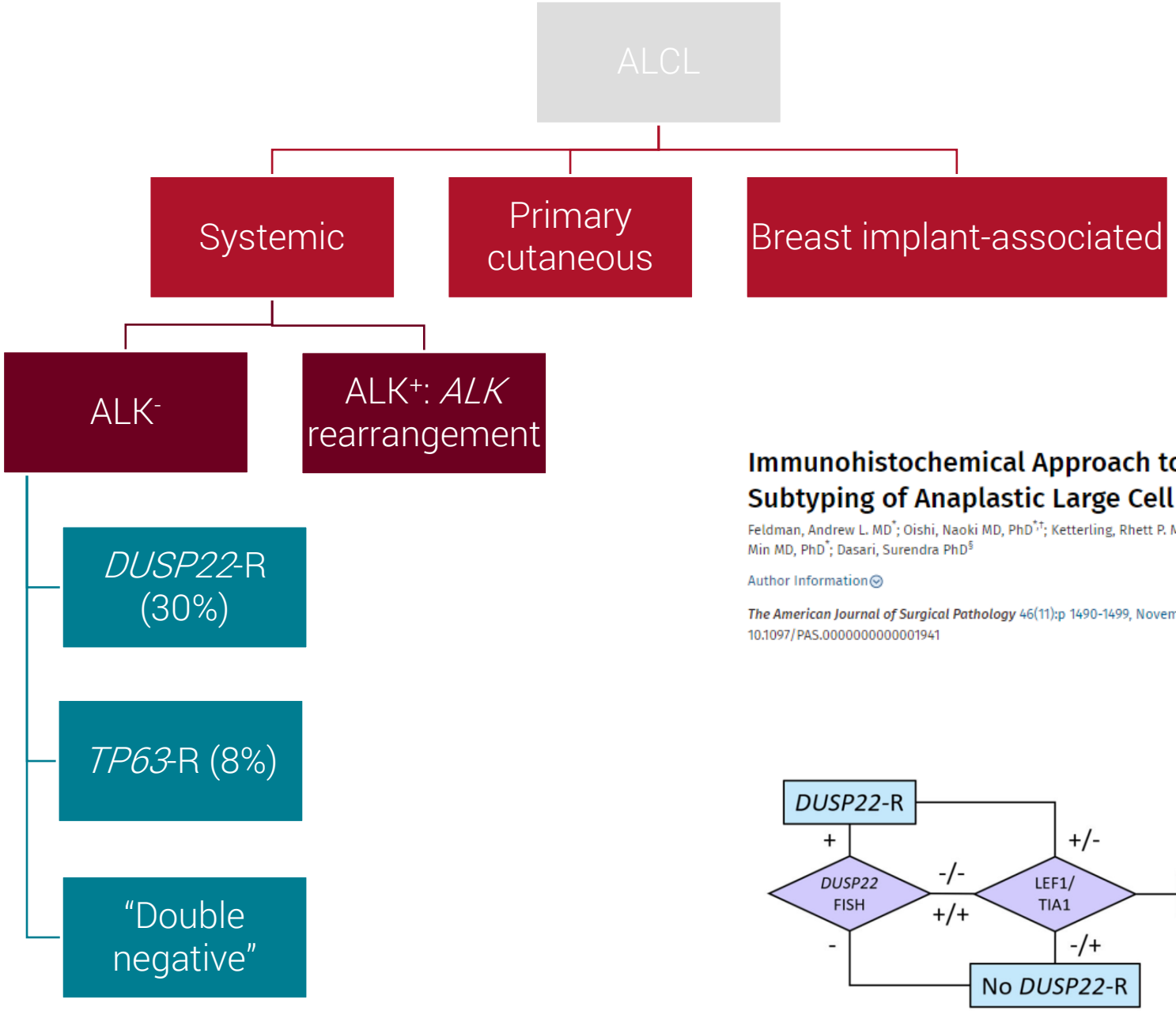
GATA3



- Luminal differentiation of breast epithelium, urothelium, trophoblast
- Master transcriptional regulator for Th2 cells
  - » Confirm T-cell lineage
  - » Part of PTCL algorithm



Amador C, Greiner TC, Heavican TB, et al. Reproducing the molecular subclassification of peripheral T-cell lymphoma-NOS by immunohistochemistry. Blood. 2019 Dec 12;134(24):2159-2170.



Immunohistochemical Approach to Genetic Subtyping of Anaplastic Large Cell Lymphoma

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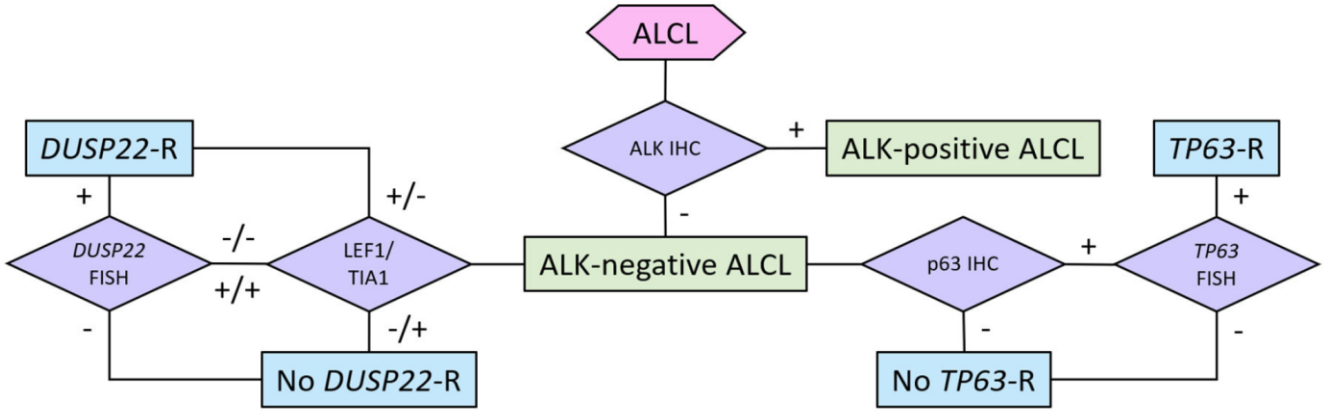

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ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes

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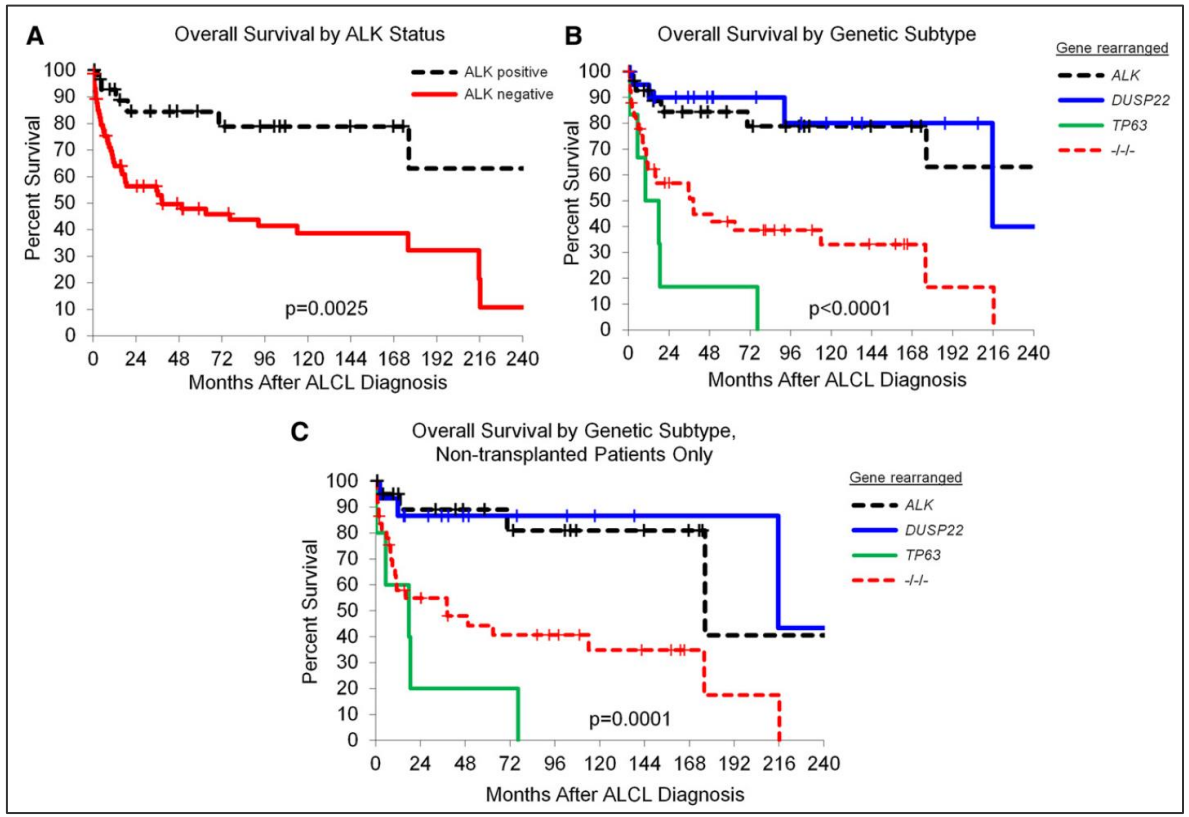

DUSP22 rearrangement is associated with a distinctive immunophenotype but not outcome in patients with systemic ALK-negative anaplastic large cell lymphoma

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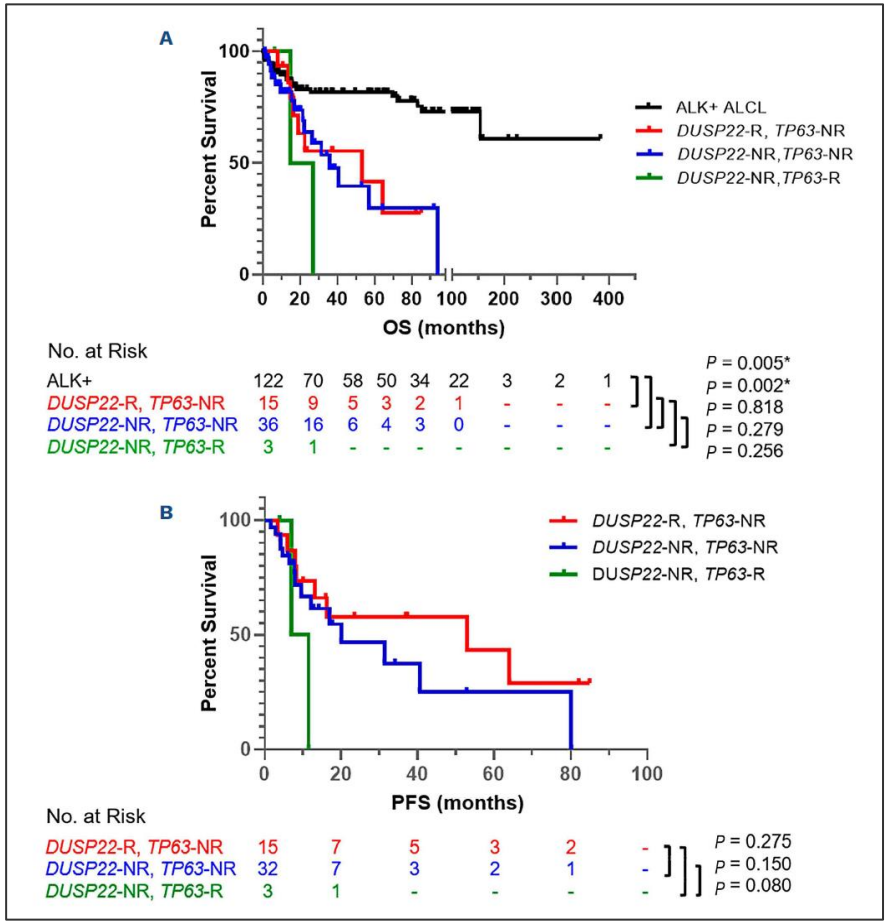
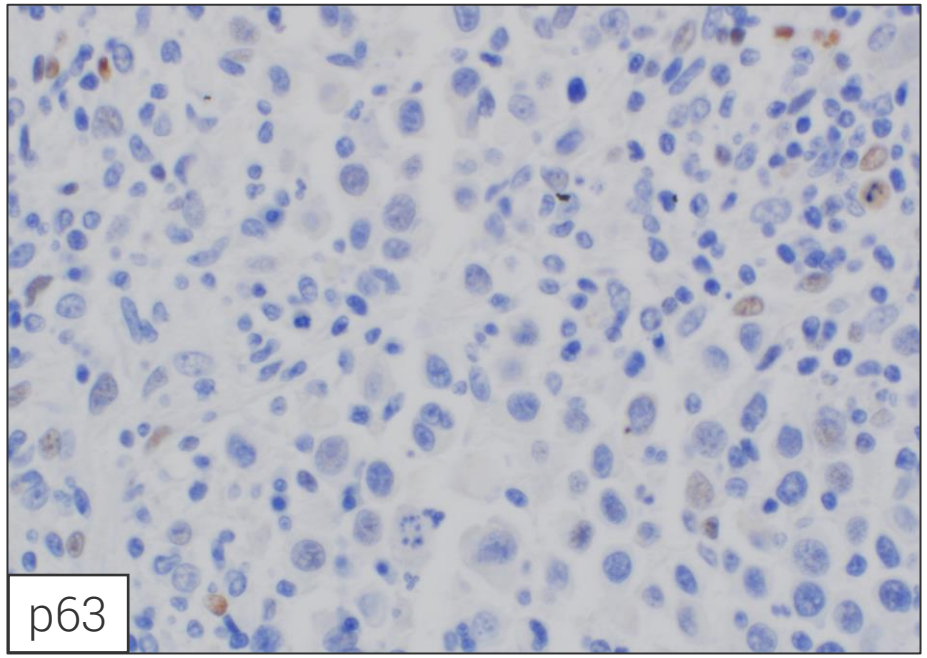
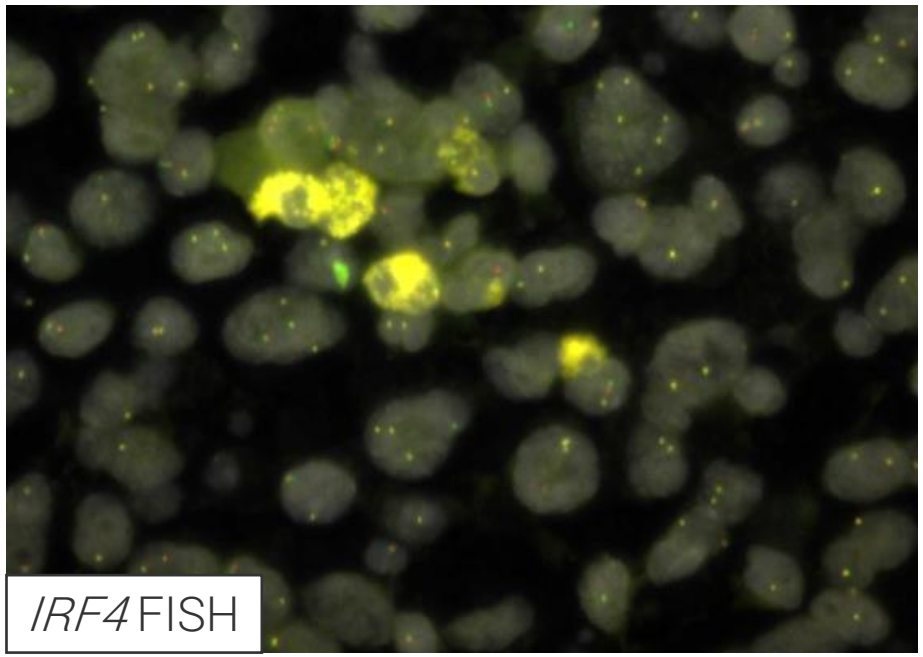






Diagnosis

ALCL ALK-negative

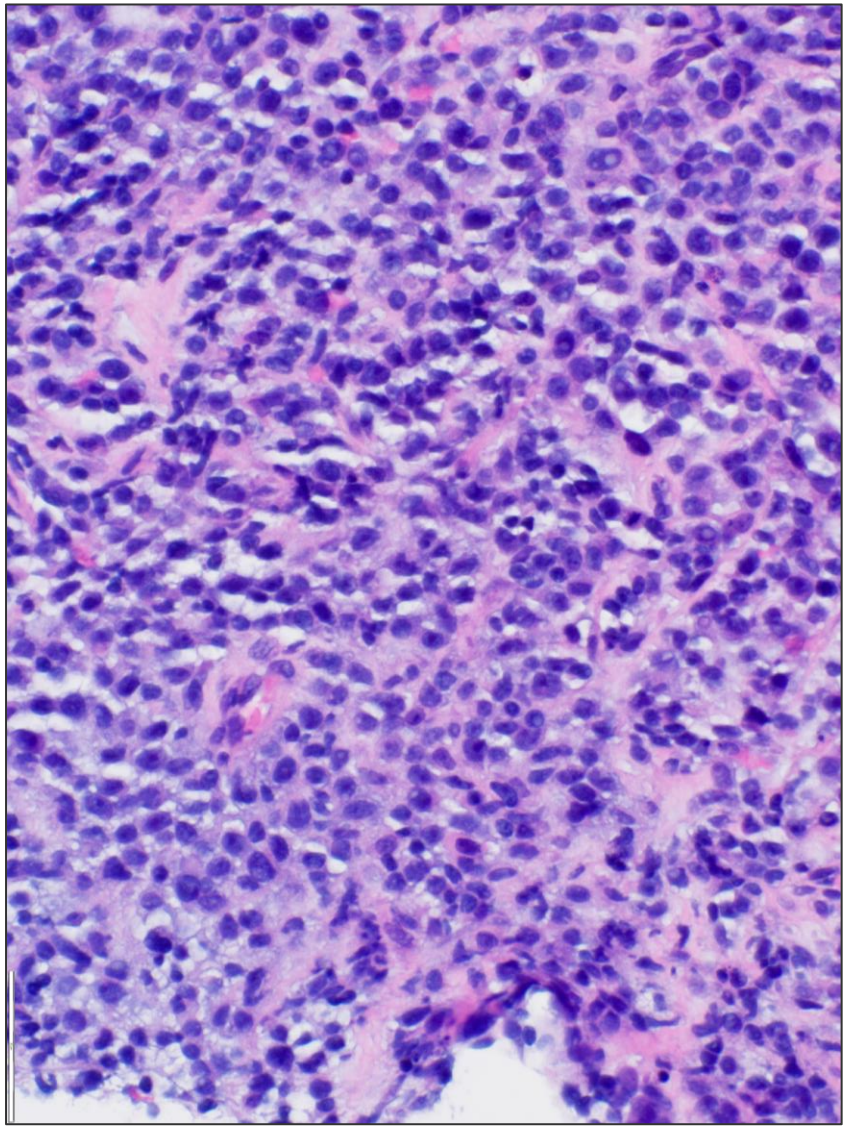
"null type"

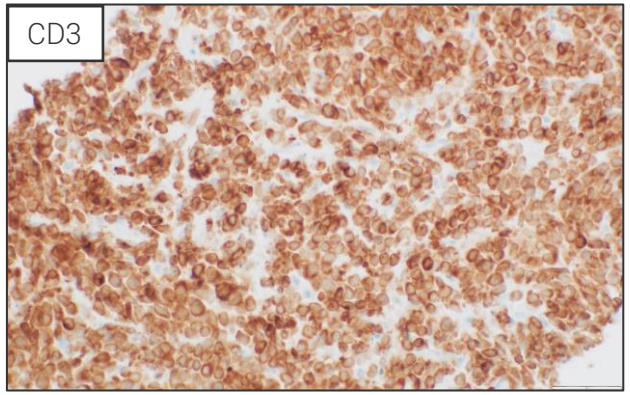
DUSP22-not rearranged

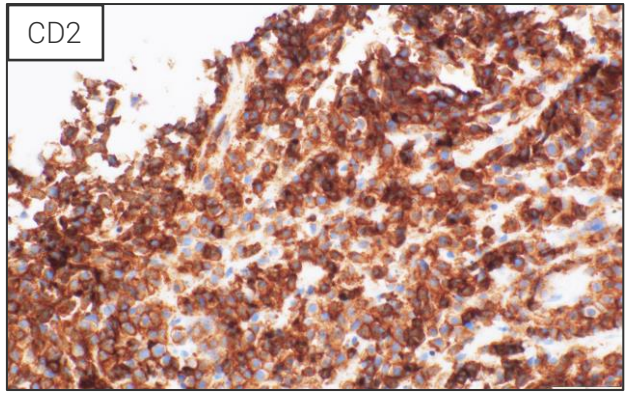
likely "double-negative"

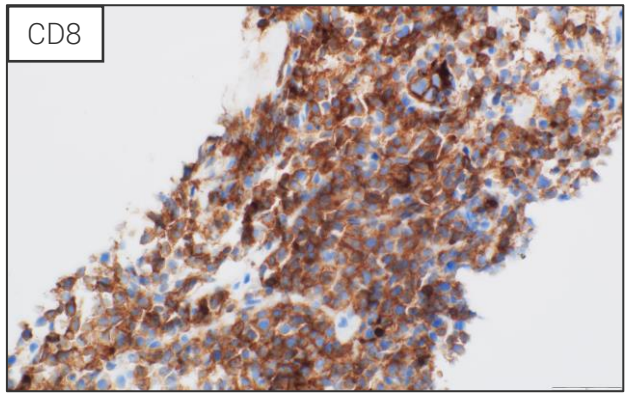
CASE FOR COMPARISON

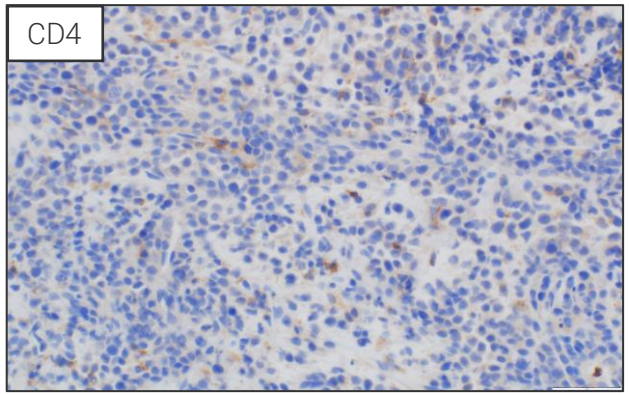
Male patient in his 70s with metastatic esophageal cancer

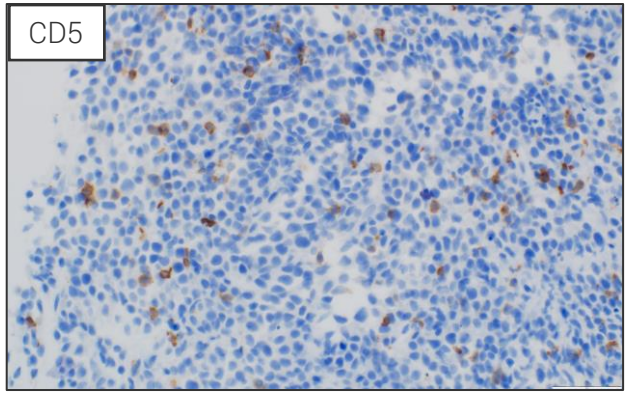


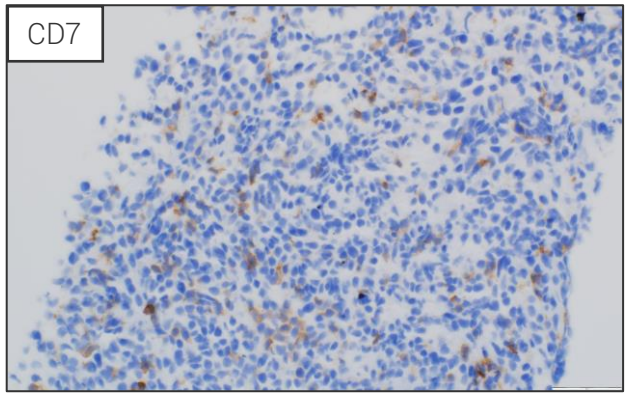




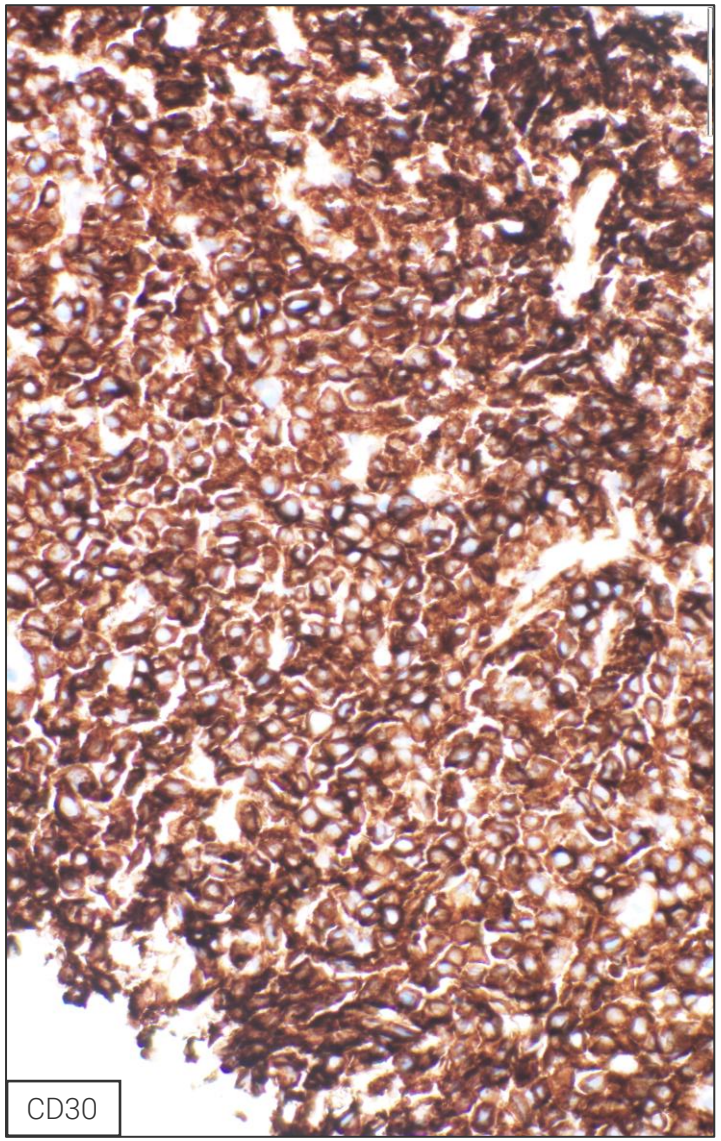


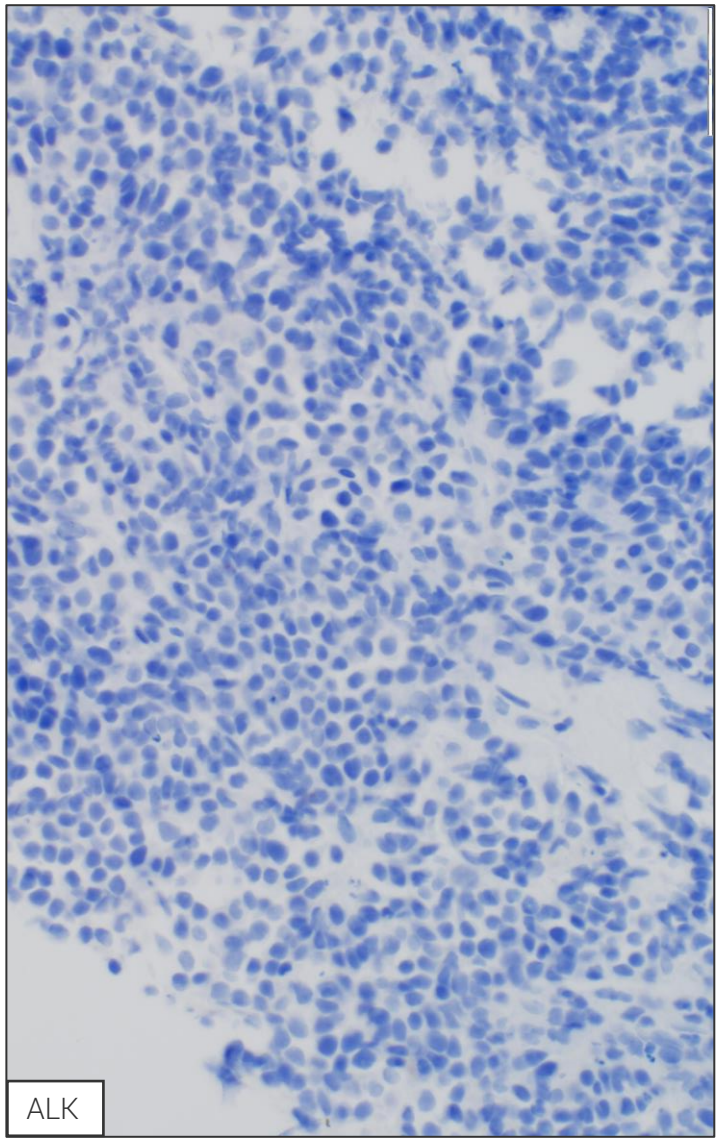






CASE FOR COMPARISON





Diagnosis
Mature T-cell lymphoma,
CD30-positive

Arch Pathol Lab Med. 2023;147:79-86.

Best Practices in CD30 Immunohistochemistry Testing, Interpretation, and Reporting

An Expert Panel Consensus

Alejandro A. Gru, MD; Megan S. Lim, MD, PhD; Ahmet Dogan, MD, PhD; Steven M. Horwitz, MD; Jan Delabie, MD, PhD; Kai Fu, MD, PhD; Deniz Peker, MD; Vishnu V. B. Reddy, MD; Mina L. Xu, MD; Kiran Vij, MD; Graham W. Slack, MD; Roberto N. Miranda, MD; Deepa Jagadeesh, MD; Julie M. Lisano, PharmD; Eric D. Hsi, MD; Emina Torlakovic, MD, PhD

Table 2. Summary of Expert Recommendations

Testing Purpose and Parameters	Recommendation
Diagnostic	CD30 testing is required for all patients in whom cHL and PTCL are differential diagnostic considerations. CD30 testing is useful for a suspected subset of large B-cell lymphomas such as gray zone lymphoma or PMBCL
Therapeutic	CD30 testing is recommended for all patients with a diagnosis of T-cell lymphoma
	In selected cases if CD30-directed therapy is being considered, then CD30 testing is useful for R/R DLBCL or PMBCL
How to test	IHC testing is the preferred methodology
Readout of the test results	Report CD30 expression based on what is observed at any staining intensity (membrane, cytoplasmic, and Golgi-type staining or any combination of these are acceptable)
	Estimate percent positive expression in tumor cells (when possible) or total cells (when challenging to separate tumor from nontumor cells) and report in numeric number or range
	Record descriptively if nontumor cells are positive
Interpretation and reporting of test results	For diagnostic purposes, the interpretation and reporting of the CD30 results should follow published diagnostic guidelines
	For therapeutic information, pathologist reports what is observed both in tumor cells and microenvironment; oncologist interprets reported results in the context of published results of clinical trials and patient's specific/personal clinical context

IHC markers

	Diagnostic markers	Predictive markers
Purpose	Make a diagnosis	Predict response to particular therapy
End-user	Pathologist	Clinician
Reporting	Usually POS vs NEG	Detailed information: - % pos/neg tumor cells - % pos/neg non-tumor cells - intensity of expression - pattern of expression
Validation	10 positive and 10 negative Concordance ≥90%	20 positive and 20 negative Concordance ≥90%
Proficiency testing		Necessary If only technical or professional components are performed, alternative performance assessment

PATIENT 2

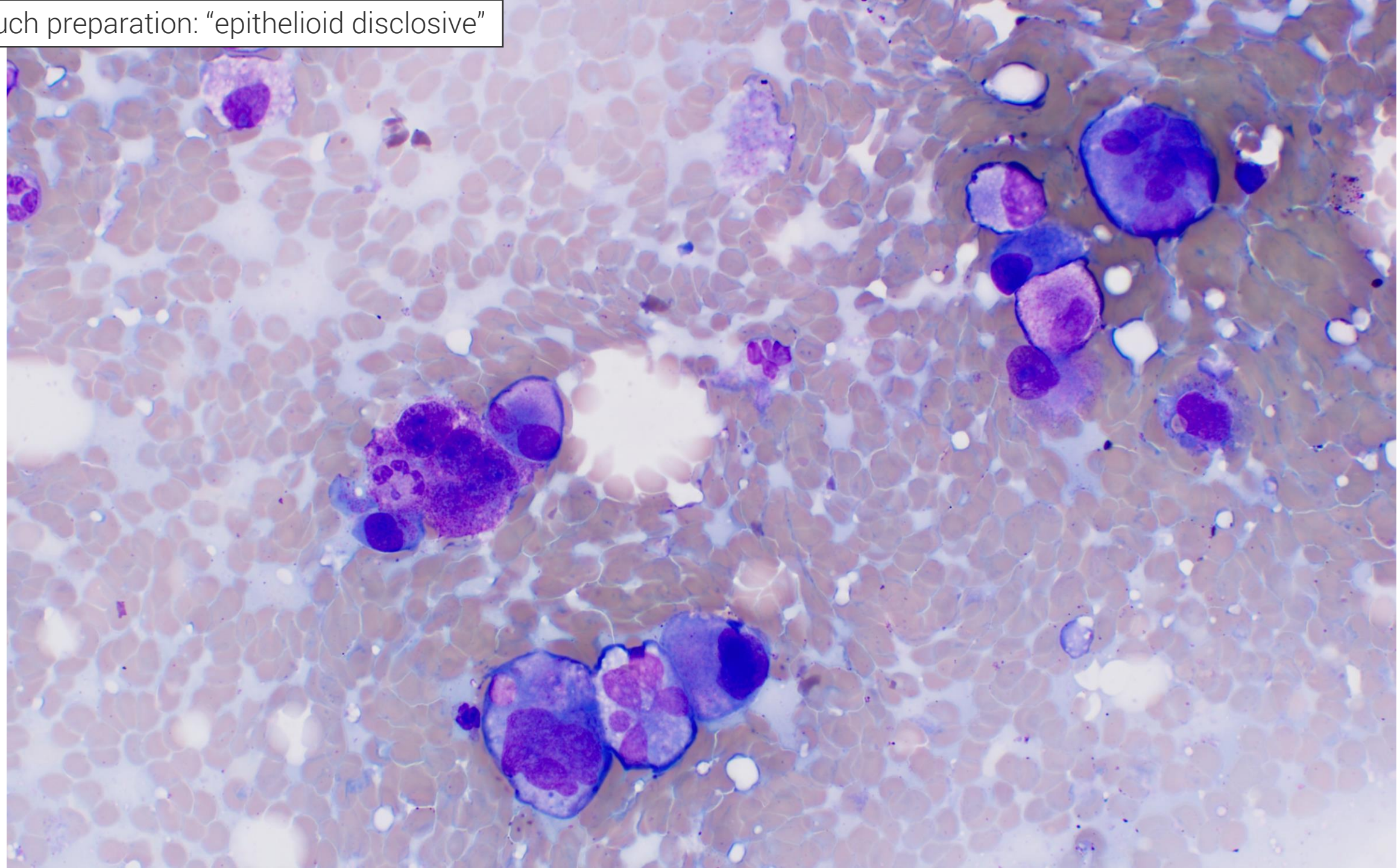
Male in his 60's with a lytic lesion in femur

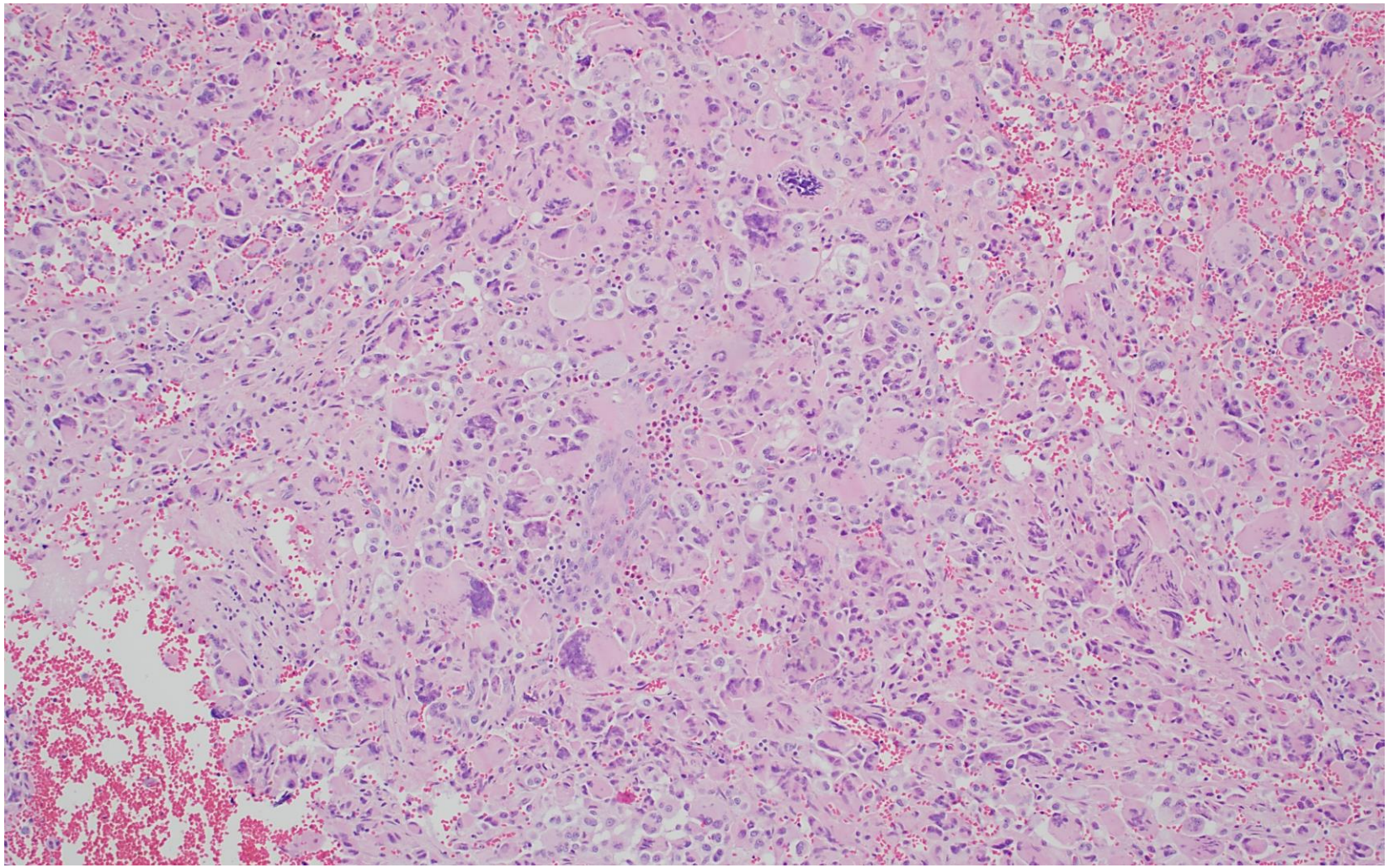
- Past medical Hx:
  - » "Testicular tumor"
  - » Lung cancer
  - » Small monoclonal IgA-kappa protein

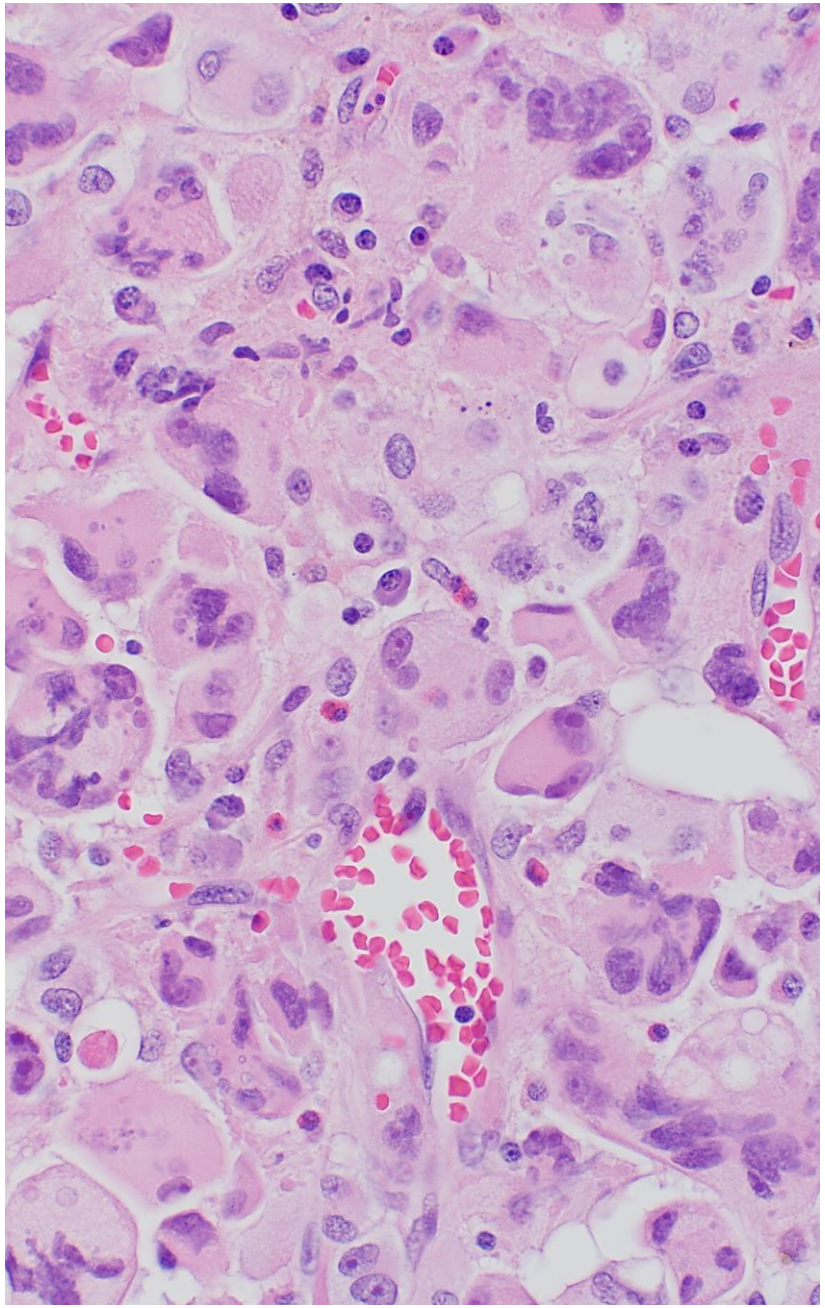
Ancillary studies:

- Imaging: 5 cm lytic lesion with exuberant periosteal reaction
- Flow cytometry: kappa-restricted plasma cells

Touch preparation: “epithelioid disclosive”







Differential Dx

- Metastatic carcinoma
- Recurrent/metastatic germ ell tumor
- Plasma cell neoplasm
- Plasmablastic neoplasm

- Myeloid lineage
- Histiocytic lineage: histiocytic sarcoma, Langerhans cell histiocytosis
- Mast cell lineage
- B-cell lineage: classic Hodgkin lymphoma
- T-cell lineage: ALCL
- Plasmacytoid dendritic cells: blastic plasmacytoid dendritic cell neoplasm
- Non-hematopoietic:
  - » Epithelial: germ cell tumor, etc.
  - » Soft tissue: sarcoma
  - » Melanoma

IHC workup

- Epithelial: AE1/3^{-}, SALL4^{-}, PAX8^{-}
- Melanoma: S100^{-}
- Hematopoietic: CD45$^{\text{variable}}$
- B-/T-cells: CD138^{-}, CD20^{-}, PAX5^{-}, CD79a^{-}, CD3^{-}, CD56^{-}, CD2^{-}, CD25^{-}
- Myeloid/erythroid: MPO^{-}, CD34^{-}, CD117^{+}, CD33^{+}, E-cadherin^{-}, Glycophorin A^{-}, CD61^{-}
- Histiocytes: CD4^{+}, CD68^{-}, lysozyme^{-}
- Other: ALK^{-}, CD56^{-}, CD35^{-}, CD30$^{\text{weak partial}}$, CD38$^{\text{partial}}$

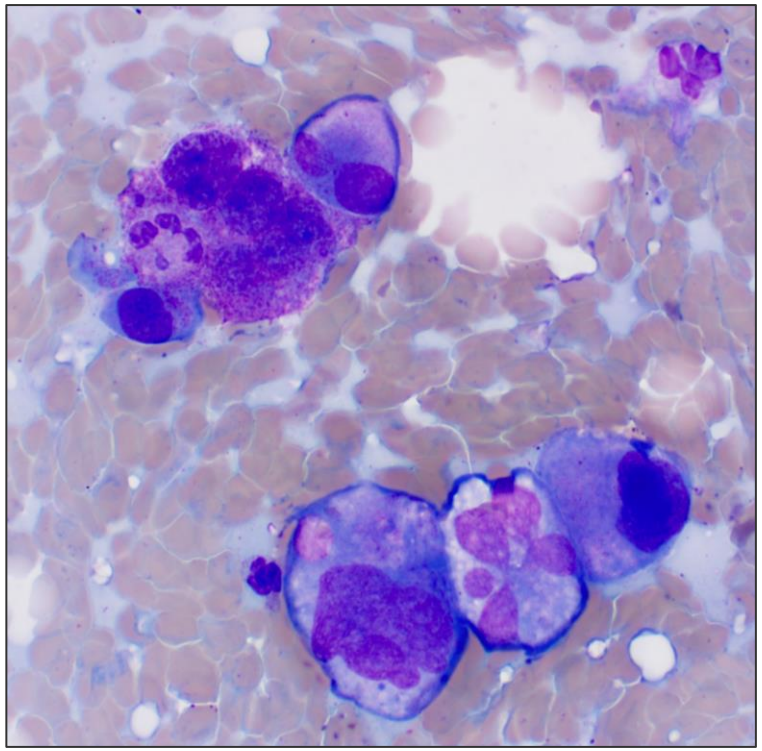
CD117

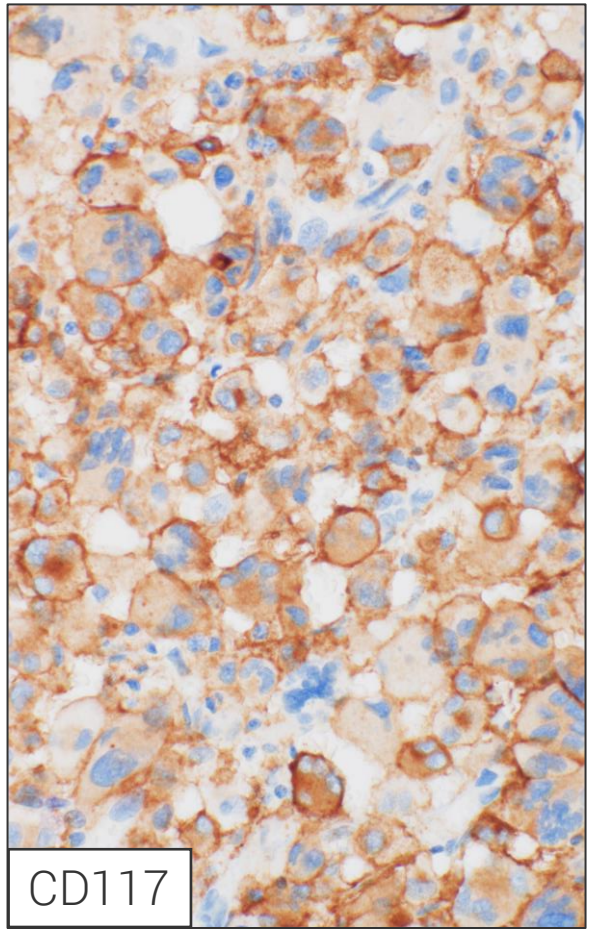
- cKIT – class III receptor tyrosine kinase
- In hematopoiesis, stem cell factor receptor and mast cell growth factor

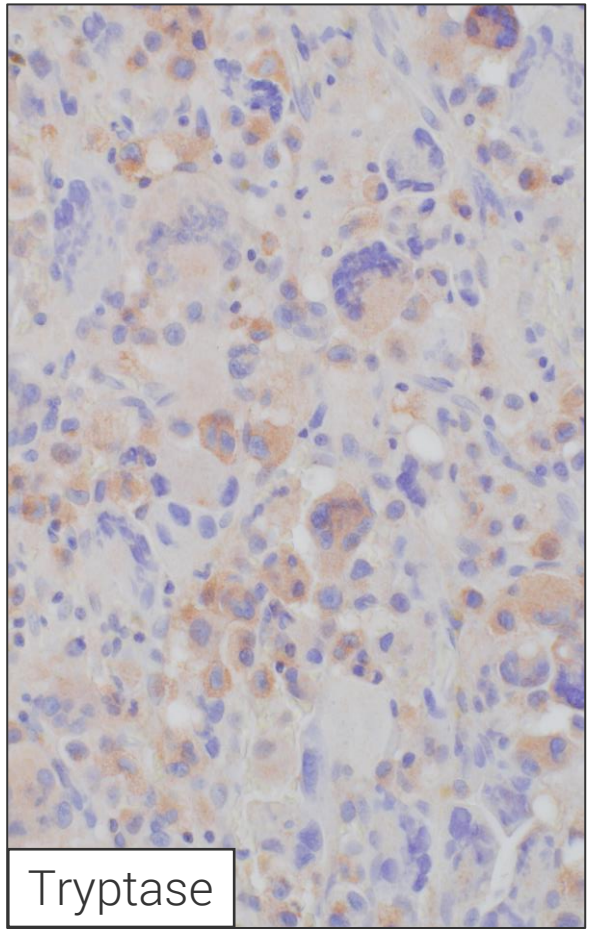
- Therapy target: TKI
  - » ‘Classic’, e.g., Imatinib
  - » ‘Multikinase’, e.g., Midostaurin
  - » ‘Selective’, e.g., Avapritinib

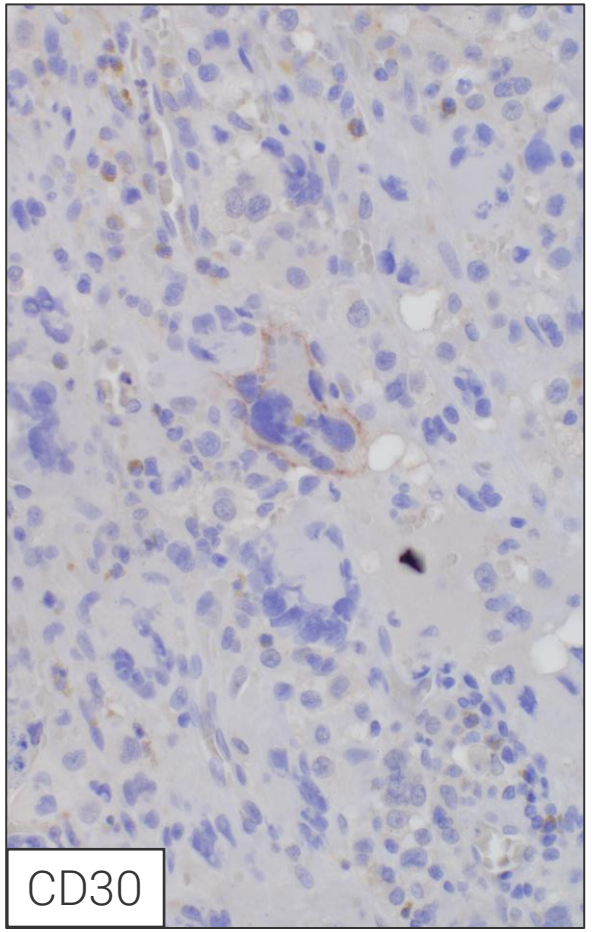
- HemePath: immature hematopoietic cells, mast cells

- SurgPath: adenoid cystic carcinoma, GIST, melanoma, seminoma/dysgerminoma




CD117


Tryptase


CD30

Mastocytosis: WHO, 2022 classification

Cutaneous Mastocytosis (CM)

- Maculopapular CM/urticaria pigmentosa
  - » monomorphic
  - » polymorphic
- Diffuse CM
- Cutaneous mastocytoma
  - » isolated mastocytoma
  - » multilocalized mastocytoma

* Mastocytosis in the skin (MIS)

Systemic Mastocytosis (SM)

- Bone marrow mastocytosis (BMM)
- Indolent SM (ISM)
- Smoldering SM (SSM)
- SM with associated hematological neoplasm (SM-AHN)
- Aggressive SM (ASM)
- Mast cell leukemia (MCL)

Advanced SM (AdvSM)

Mast cell sarcoma

Extracutaneous mastocytoma

Systemic mastocytosis Dx Criteria (WHO 2022 and ICC 2022)

Diagnosis requires:

- Major + 1 minor/Only major with no minor
- or 3 minor

Major criterion

- Multifocal dense infiltrates of MCs (≥15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s)

Minor criteria

1. >25% of all MCs are atypical cells (type I or type II) on BM smears or are spindle-shaped in MC infiltrates detected on sections of visceral organs
2. Activating KIT mutation (Codon 816 or other critical regions) in the BM or another extracutaneous organ
3. MCs in BM or blood or another extracutaneous organ exhibit CD2 and/or CD25 and/or CD30
4. Baseline serum tryptase level >20 ng/mL (in case of an unrelated myeloid neoplasm, this item is not valid as an SM criterion). In case of HαT, it must be adjusted.

Mast cell sarcoma

- Extremely rare disease
- Destructive growth
- Highly atypical mast cells
- Poor prognosis

- Clinical presentation
  - » Median age 50-60 (1-77 yo)
  - » Bones is the most common site of involvement (90%)
  - » MCAS in 30%
  - » Serum tryptase often elevated
  - » Most cases de-novo, 23% in association with systemic mastocytosis
  - » Has been reported to be clonally related to mediastinal germ cell tumor

Key features

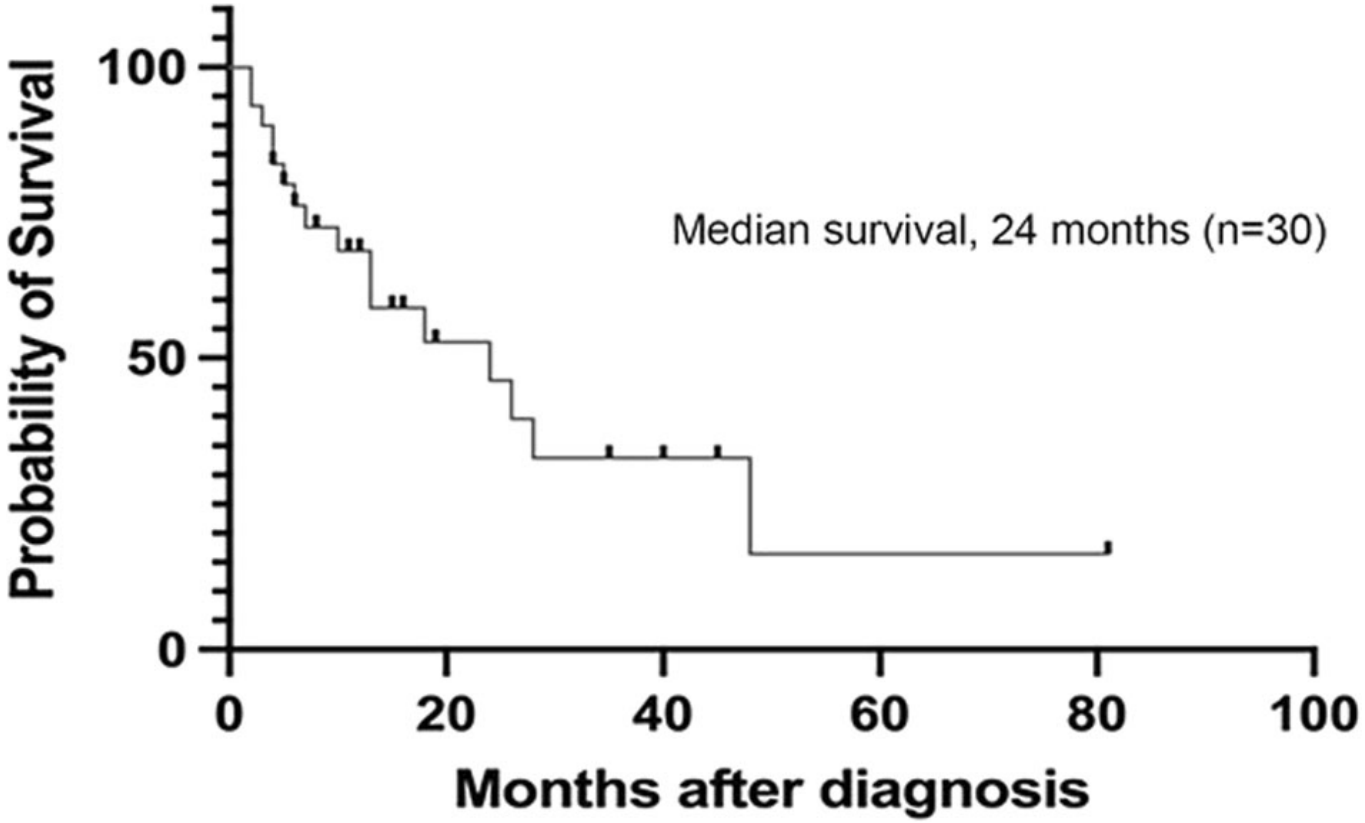
- Variable cytomorphology, often pleomorphic
- Cytoplasmic granules are often absent
- Background eosinophils

- *KIT* mutations – 29%
- *KIT*^{D816V} – 7%

- Immunophenotype
  - » CD117 – 100%
  - » Tryptase – 100%
  - » CD25 – 60%
  - » CD2 – 33%
  - » CD30 – 54%
  - » CD13 – 100%
  - » CD33 – 100%
  - » CD34 – 0%
  - » CD4 – 50%
  - » CD68 – 82%
  - » S100 – 0%
  - » CD163 – 0%

Matsumoto NP, Yuan J, Wang J, al. Mast cell sarcoma: clinicopathologic and molecular analysis of 10 new cases and review of literature. Mod Pathol. 2022 Jul;35(7):865-874.

Prognosis



- Treatment
  - » Excision ± radiation
  - » Many are resistant to imatinib, dasatinib, or midostaurin
  - » Heme chemotherapy of limited effect

Matsumoto NP, Yuan J, Wang J, al. Mast cell sarcoma: clinicopathologic and molecular analysis of 10 new cases and review of literature. Mod Pathol. 2022 Jul;35(7):865-874.

PATIENT 3

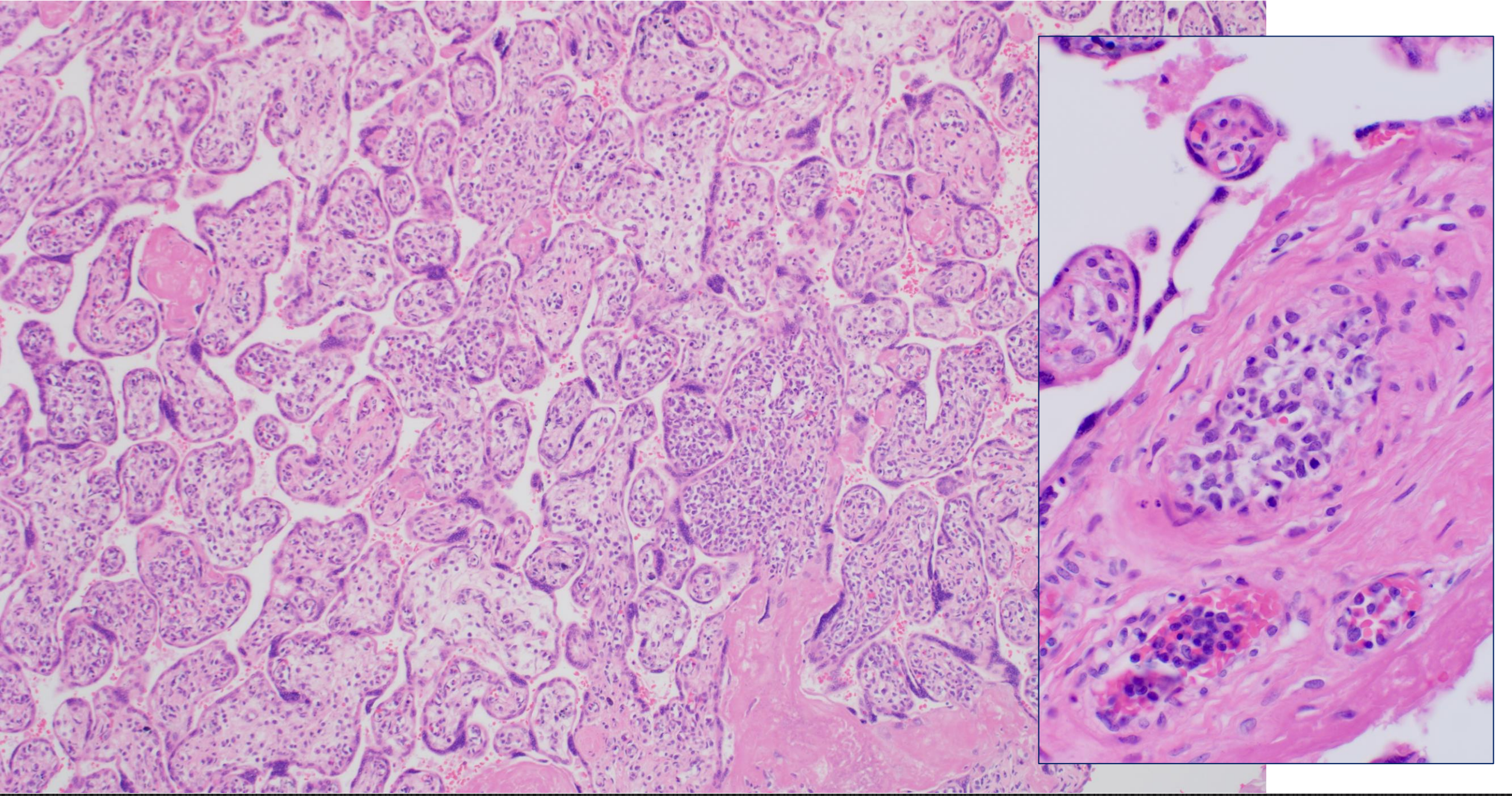
Female fetus at 36 weeks of gestation

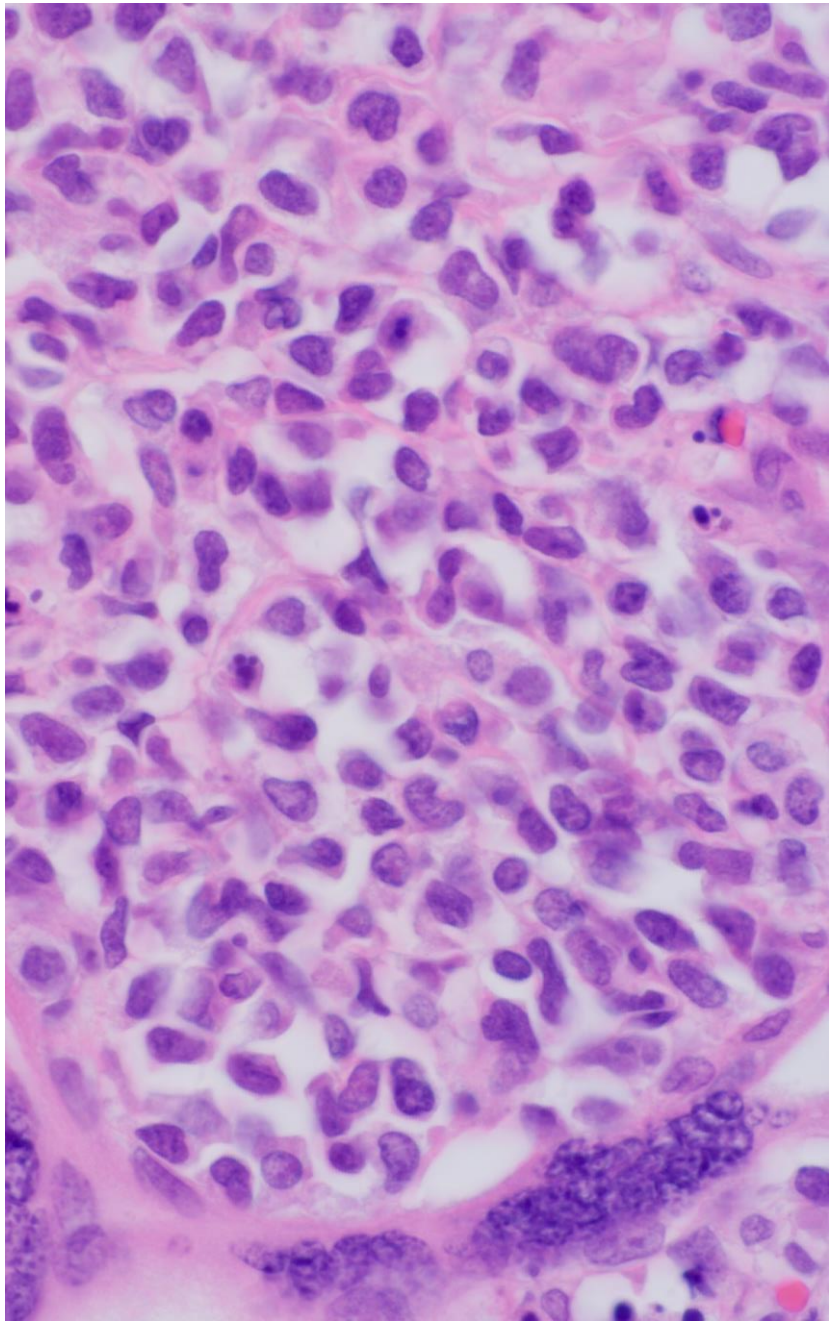
- Gravida: normal prenatal labs and course
- US 2 weeks prior admission: polyhydramnios without anatomic abnormalities
- One week prior: decreased movements

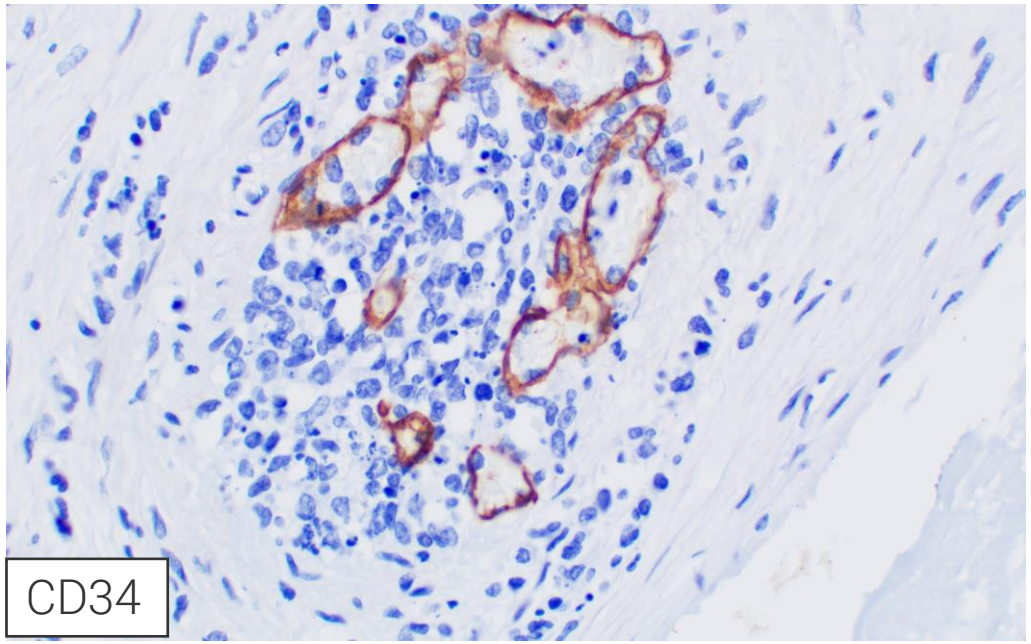
Autopsy results:

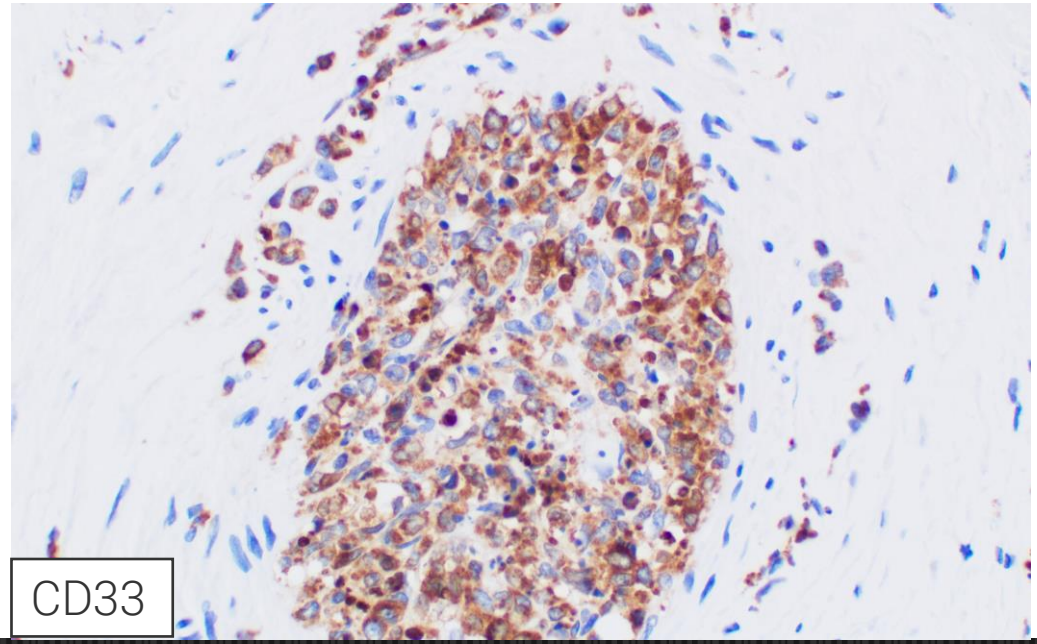
- No dysmorphisms

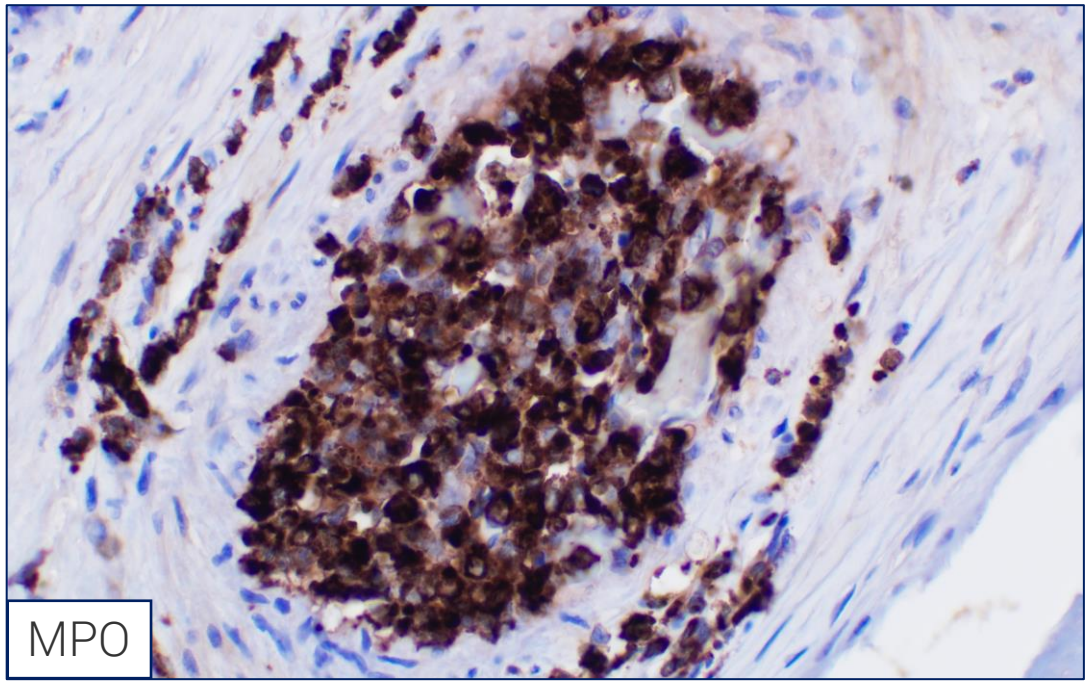
- Atypical infiltrate diffusely present in soft tissues and organ parenchyma

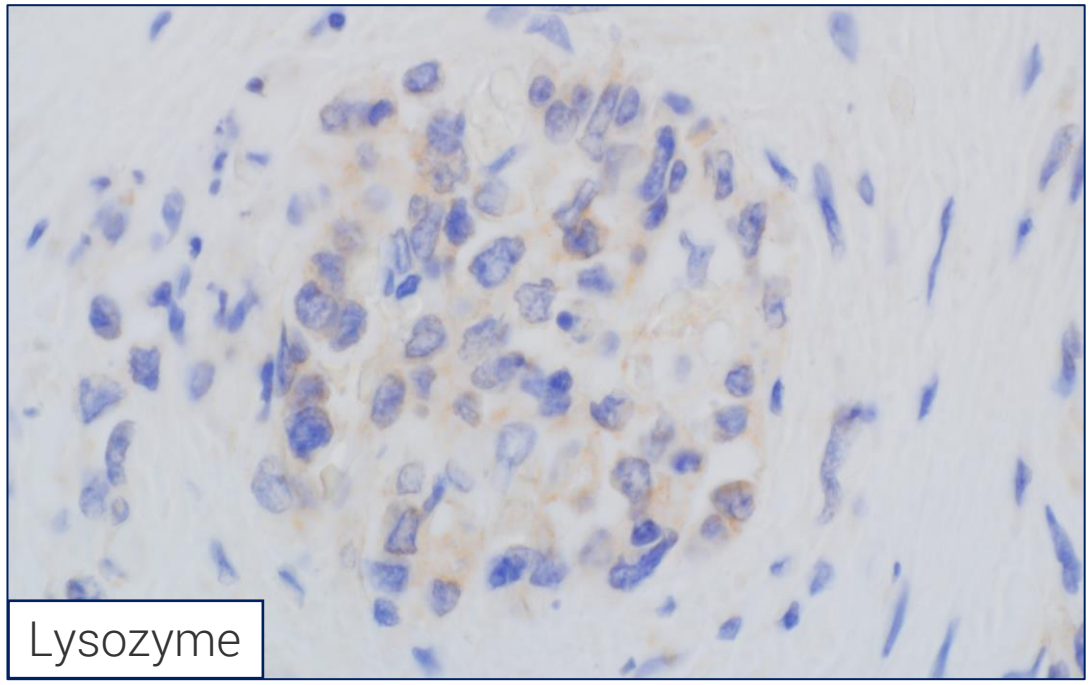


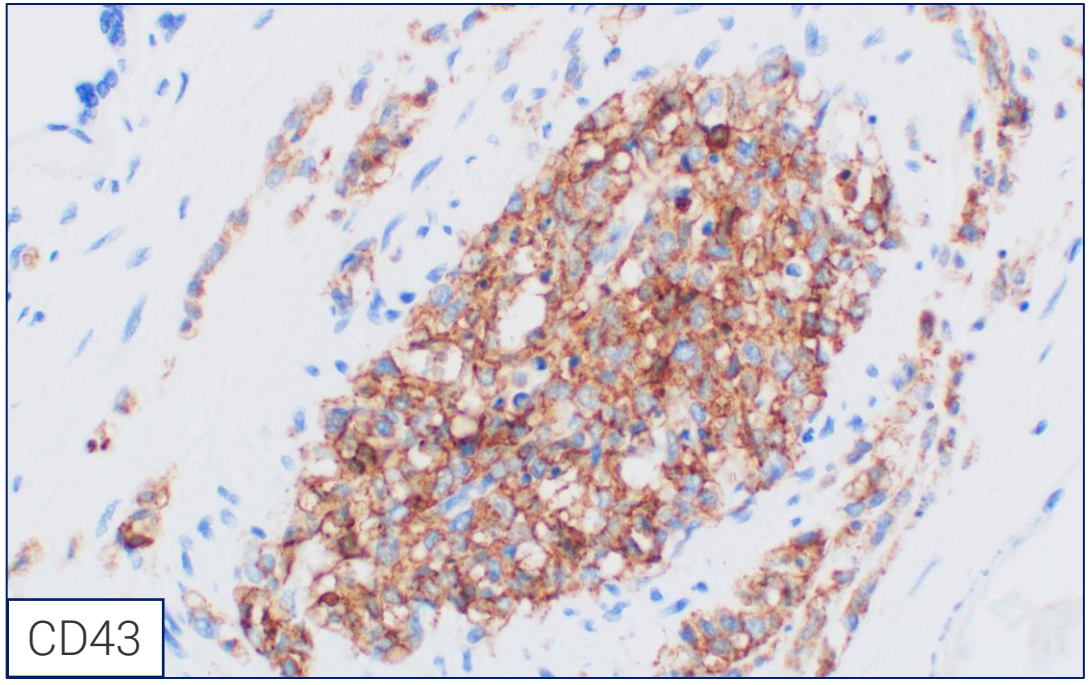


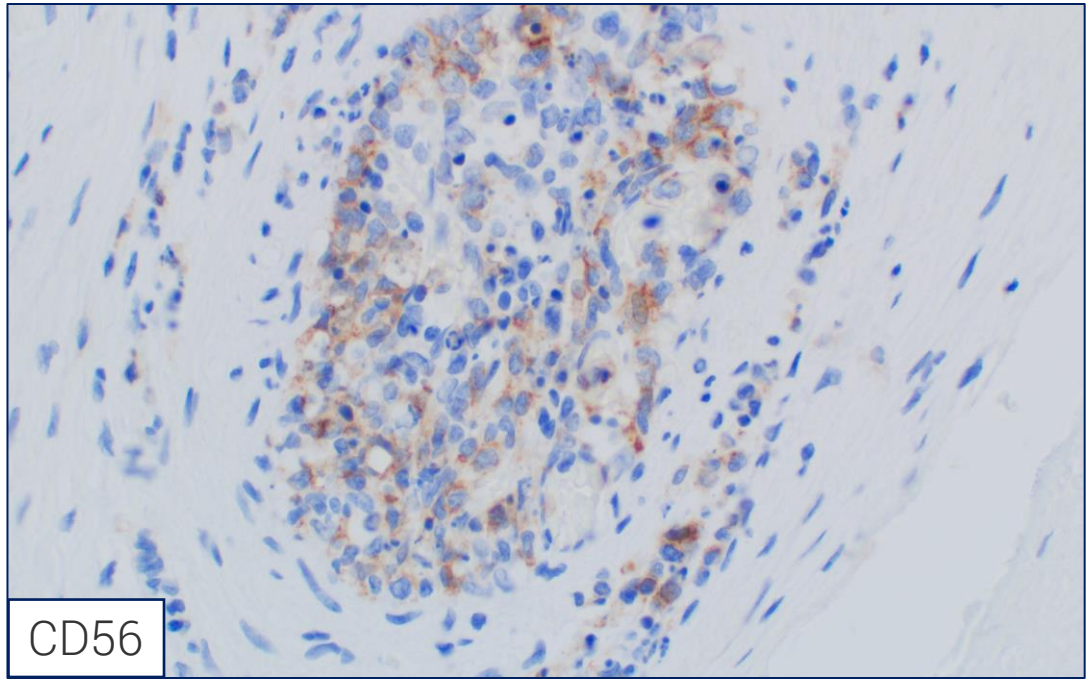

CD34


CD33


MPO


Lysozyme


CD43


CD56

Congenital leukemia

- Rare disease
- Proliferation of immature myeloid, lymphoid, or erythroid cells within 4 weeks of life
- Infiltration of non-hematopoietic tissues
- Absence of other disease that can explain this proliferation
- High mortality: 68-74%

- More commonly myeloid

Frequency:

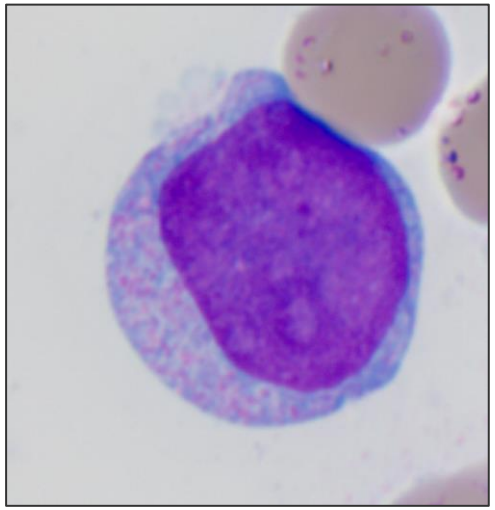
  - » M5 (monoblastic/monocytic) is the most common subtype, 60%
  - » M4 (myelomonocytic)
  - » M7 (megakaryoblatic)

- Rearrangement of *KMT2A* 11q23 in >90%

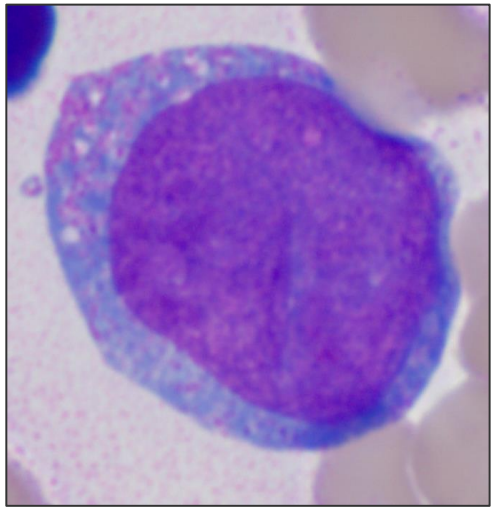
Green K et al. Congenital acute myeloid leukemia: challenges and lessons. A 15-year experience from the UK. Leuk Lymphoma. 2021 Mar;62(3):688-695.

Monocytic lineage

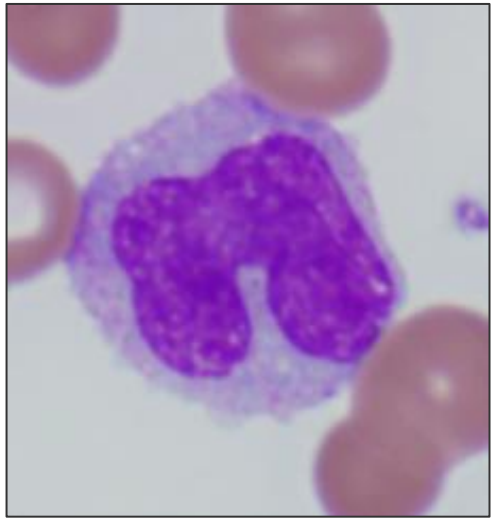
Monoblast

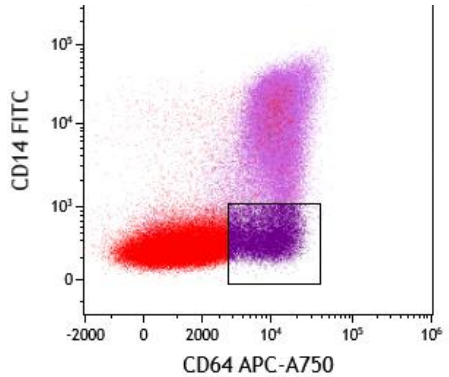


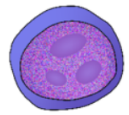
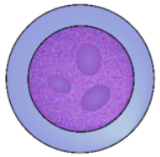
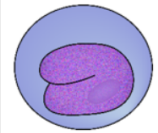
Promonocyte



Monocyte





LearnHaem Haematology made simple Cell/Marker	 CD34+ Blast	 CD34 dim Monoblast	 Promonocyte	 Monocyte
SSc	Low	Int	Int	Int
CD45	+	+	+	Bright
CD34	+	Dim	-	-
MPO	+	Variable	Variable	+
HLA-DR	+	Bright	Bright	+
CD117	+	+	Dim	-
CD13	+	+	+	Bright
CD16	-	-	-	-
CD11b	-	-	-	+
CD10	-	-	-	-
CD64	-	+	Bright	Bright
CD35	-	-	+	Bright
IREM2 (CD300e)	-	-	-	Bright
CD14	-	-	-	+
CD105	-	-	-	-
CD36	-	-	+	+
CD33	+	+	+	Bright
CD71	-	-	-	-
CD56	-	-	-	-
CD15	-	-	-	Dim
CD38	+	+	+	+
CD4	-	+	+	+
CD25	-	-	-	-
CD41a	-	-	-	-
CD42b	-	-	-	-
CD9	-	-	-	-

https://www.learnhaem.com/monocyte-maturation-table/

IRF8

Interferon Regulatory Factor-8 – lineage-specific transcription factor for B-cells and monocytes/dendritic cells

ORIGINAL ARTICLE

IRF8 is a Reliable Monoblast Marker for Acute Monocytic Leukemias

Samuel G. Katz, MD, PhD, Susmitha Edappallath, MD, and Mina L. Xu, MD

Am J Surg Pathol • Volume 45, Number 10, October 2021

AMoL (n=90)

CML (n=23)

AML non-Mo (n=26)

Normal BMs (n=18)

High correlation (R=0.95) between IRF8 and blast counts in AMoL

Good correlation (R=0.86) in CMML

No correlation in other settings

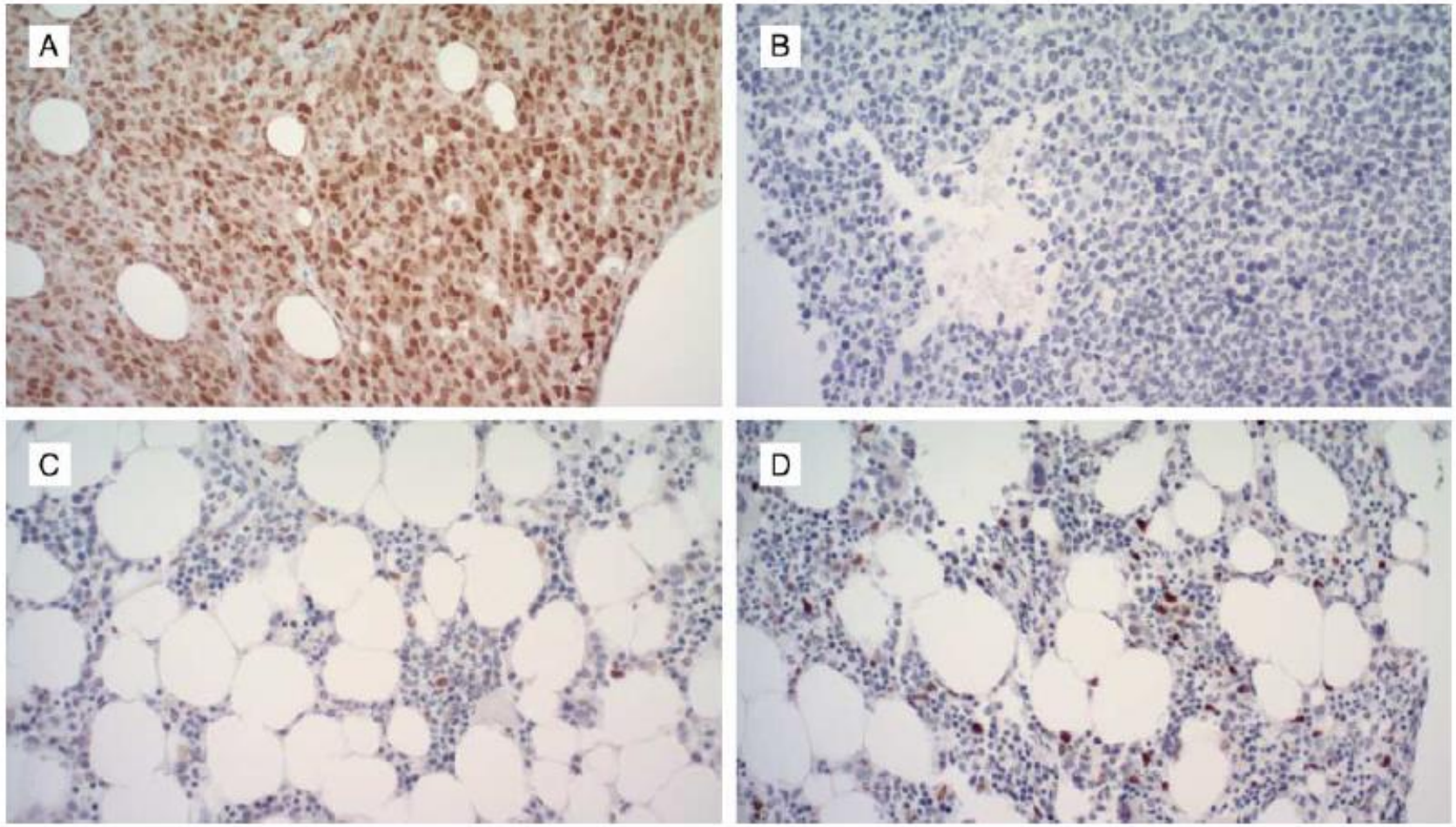


FIGURE 2. IRF8 expression in bone marrow trephine core biopsies in (A) AMoL, (B) normal staging marrow, (C) residual disease negative <5% blasts, and (D) residual disease positive 10% blasts.

Positive:
Hematogones (variable)
Some B-cells (variable)
Monoblasts and promonocytes (strong to weak)
pDCs (strong)

Negative:
Mature monocytes

Table 2 IRF8 expression in normal tissues and malignancies of different differentiation included in a pan-cancer TMA.

Tissue	Subtype	Negative	Positive	Total
Bladder	Normal bladder	3 (100%)	0	3
	Papillary transitional cell carcinoma	1 (100%)	0	1
	Papillary urothelial cell carcinoma	4 (100%)	0	4
	Serous adenocarcinoma	1 (100%)	0	1
	Urothelial carcinoma	10 (100%)	0	10
Breast	Ductal carcinoma	9 (100%)	0	9
	Lobular carcinoma	1 (100%)	0	1
Colon	Normal colon	2 (100%)	0	2
	Adenocarcinoma	13 (100%)	0	13
Kidney	Normal kidney	3 (100%)	0	3
	Papillary renal cell carcinoma	10 (100%)	0	10
	Renal cell carcinoma	4 (100%)	0	4
Liver	Normal liver	4 (100%)	0	4
	Hepatocellular carcinoma	14 (100%)	0	14
	Mixed hepatocholangiocarcinoma	1 (100%)	0	1
Lung	Normal lung	2 (100%)	0	2
	Adenocarcinoma	7 (100%)	0	7
	Neuroendocrine carcinoma	1 (100%)	0	1
	Squamous cell carcinoma	8 (100%)	0	8
Ovary	Normal ovary	4 (100%)	0	4
	Adenocarcinoma	12 (100%)	0	12
Pancreas	Normal pancreas	3 (100%)	0	3
	Adenocarcinoma	1 (100%)	0	1
	Endocrine carcinoma	12 (100%)	0	12
	Neuroendocrine carcinoma	2 (100%)	0	2
Skin	Normal skin	2 (100%)	0	2
	Squamous cell carcinoma	14 (100%)	0	14
Stomach	Normal stomach	2 (100%)	0	2

(continued on next page)

Original contribution

Global assessment of IRF8 as a novel cancer biomarker☆

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[c] Department of Pathology, Brigham and Women's Hospital, Boston, MA, 02115, USA

Received 6 December 2021; revised 15 January 2022; accepted 17 January 2022

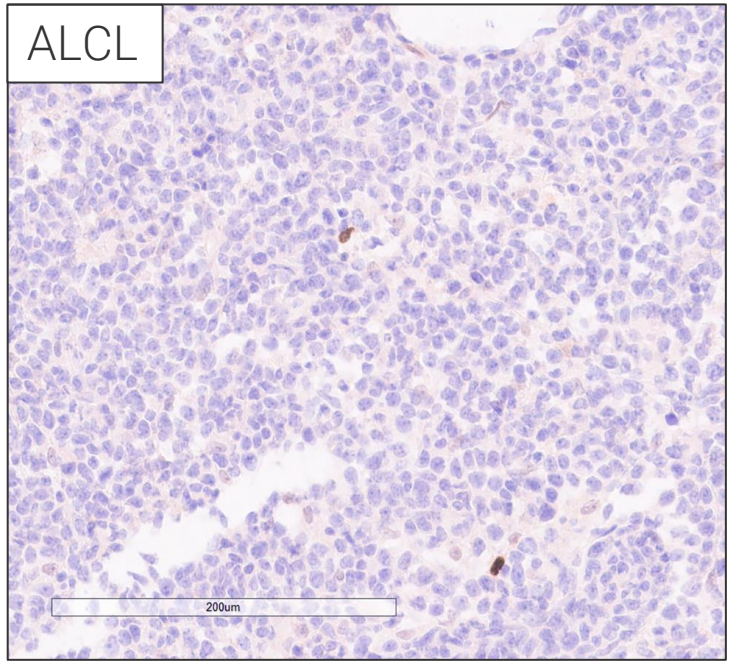
Table 2 *(continued)*

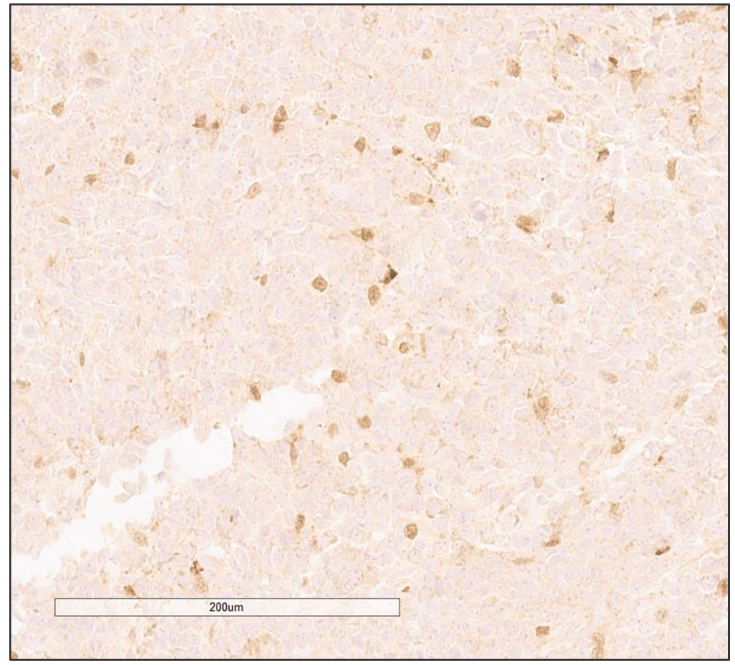
Tissue	Subtype	Negative	Positive	Total
	Adenocarcinoma	10 (100%)	0	10
Testis	Normal testis	2 (100%)	0	2
	Embryonal carcinoma	1 (100%)	0	1
	Leydig cell carcinoma	2 (100%)	0	2
	Lymphoma	0	1 (100%)	1
	Mixed germ cell carcinoma	6 (100%)	0	6
	Seminoma	5 (100%)	0	5

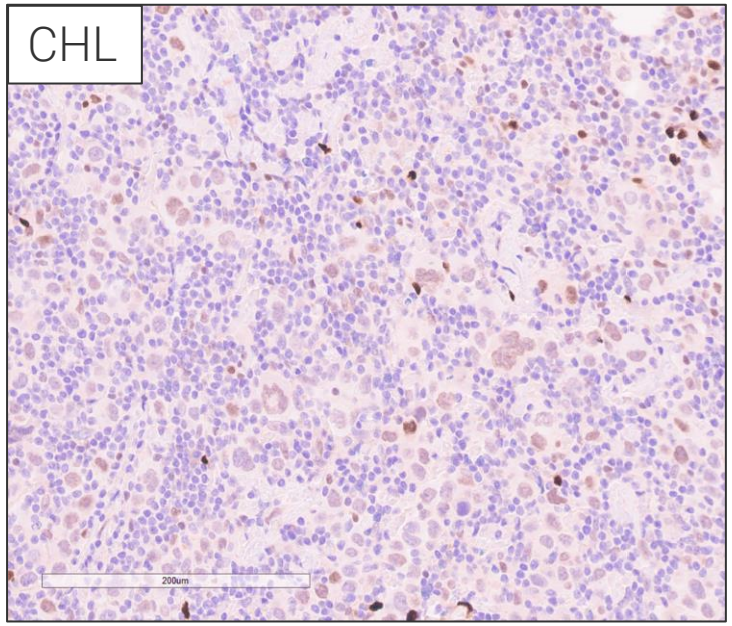
Challenging optimization

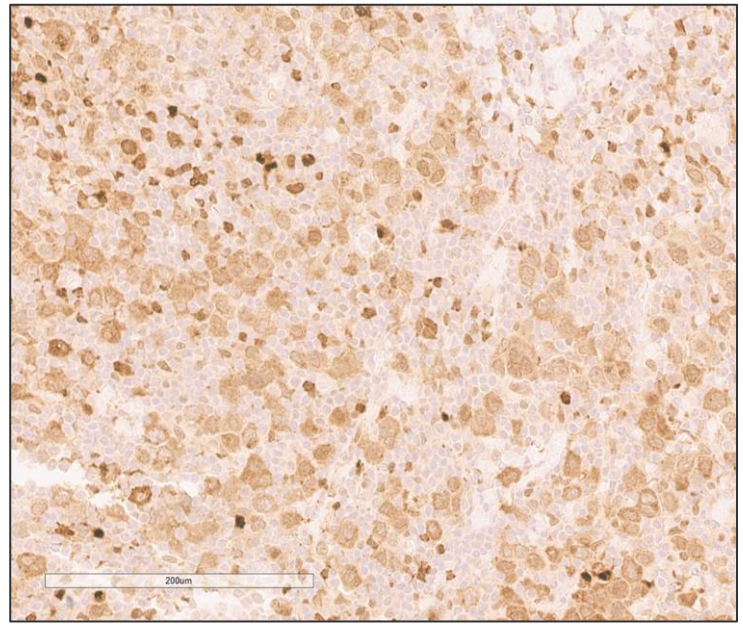
ALCLs are reportedly negative

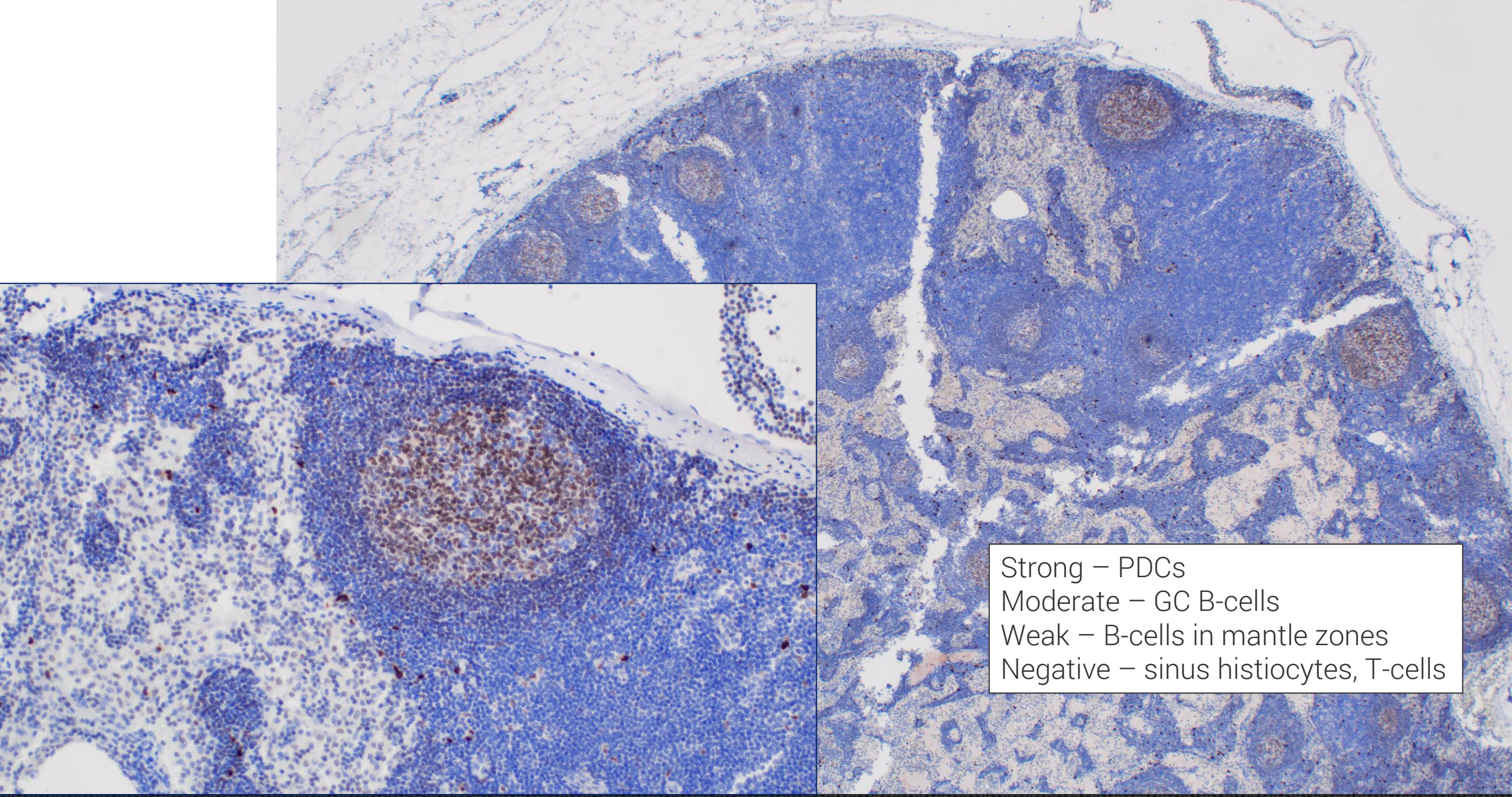
HCL are reportedly positive





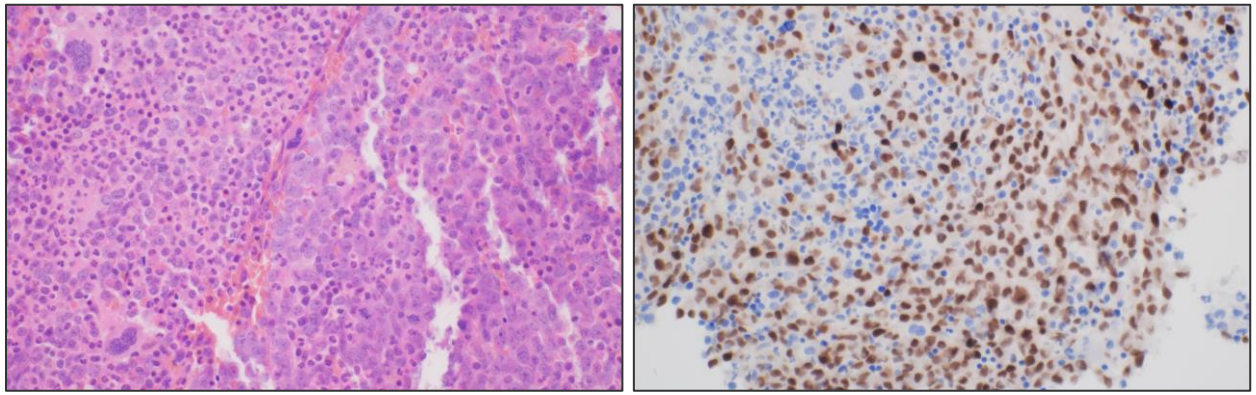




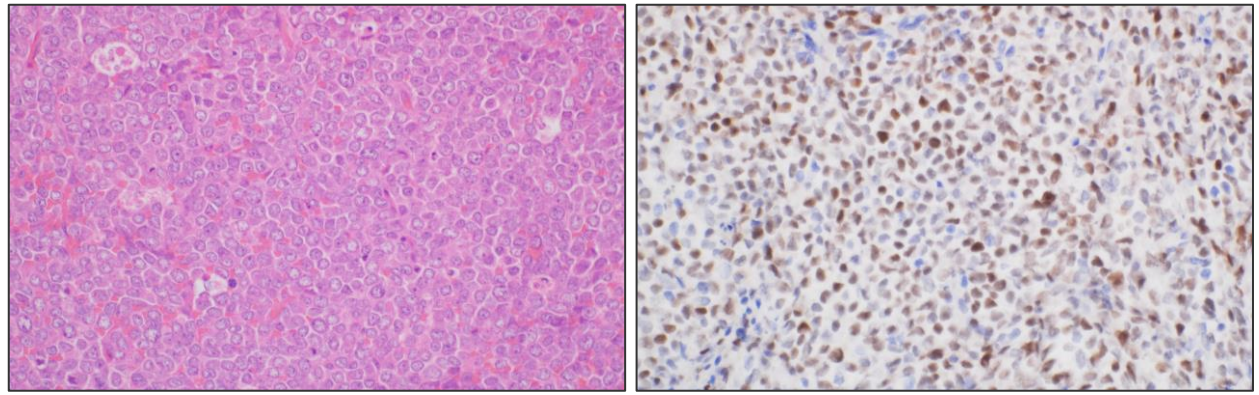


Strong – PDCs
Moderate – GC B-cells
Weak – B-cells in mantle zones
Negative – sinus histiocytes, T-cells

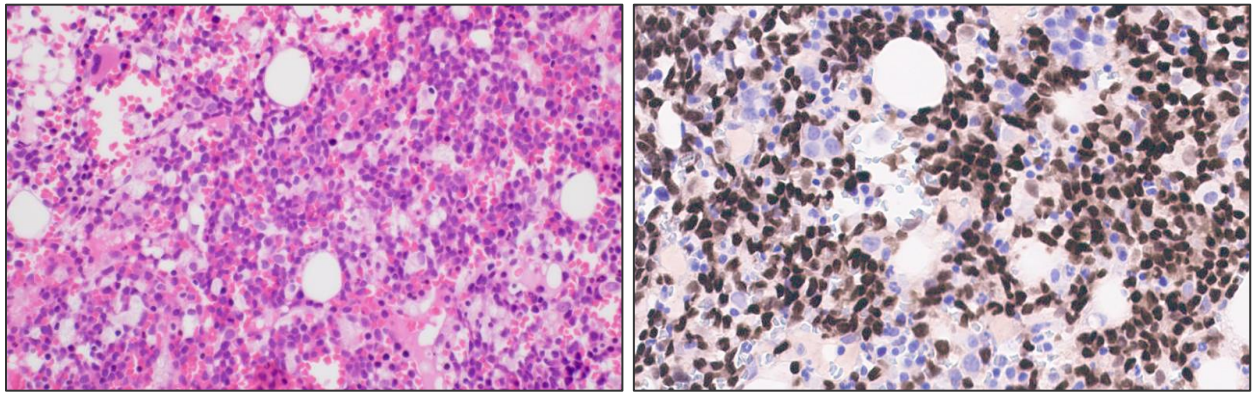
CMML to AML



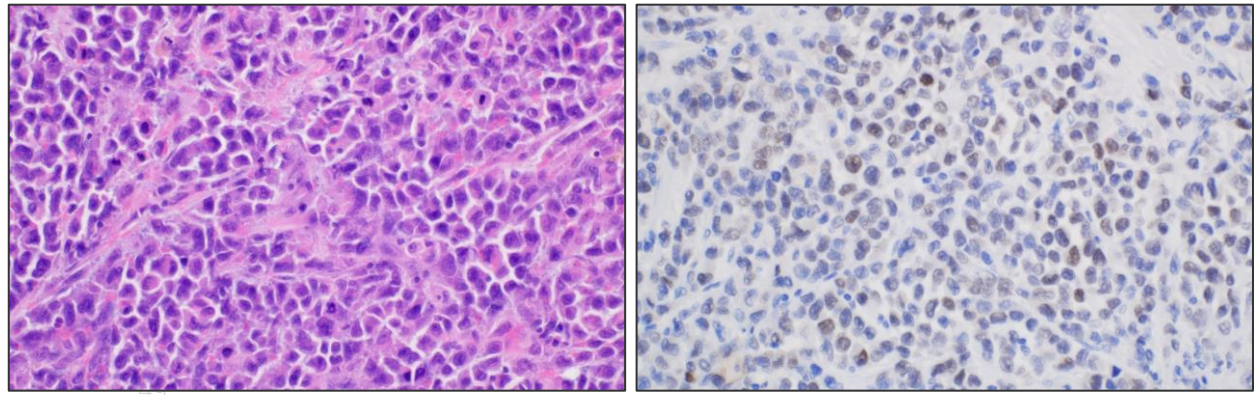
Myeloid sarcoma



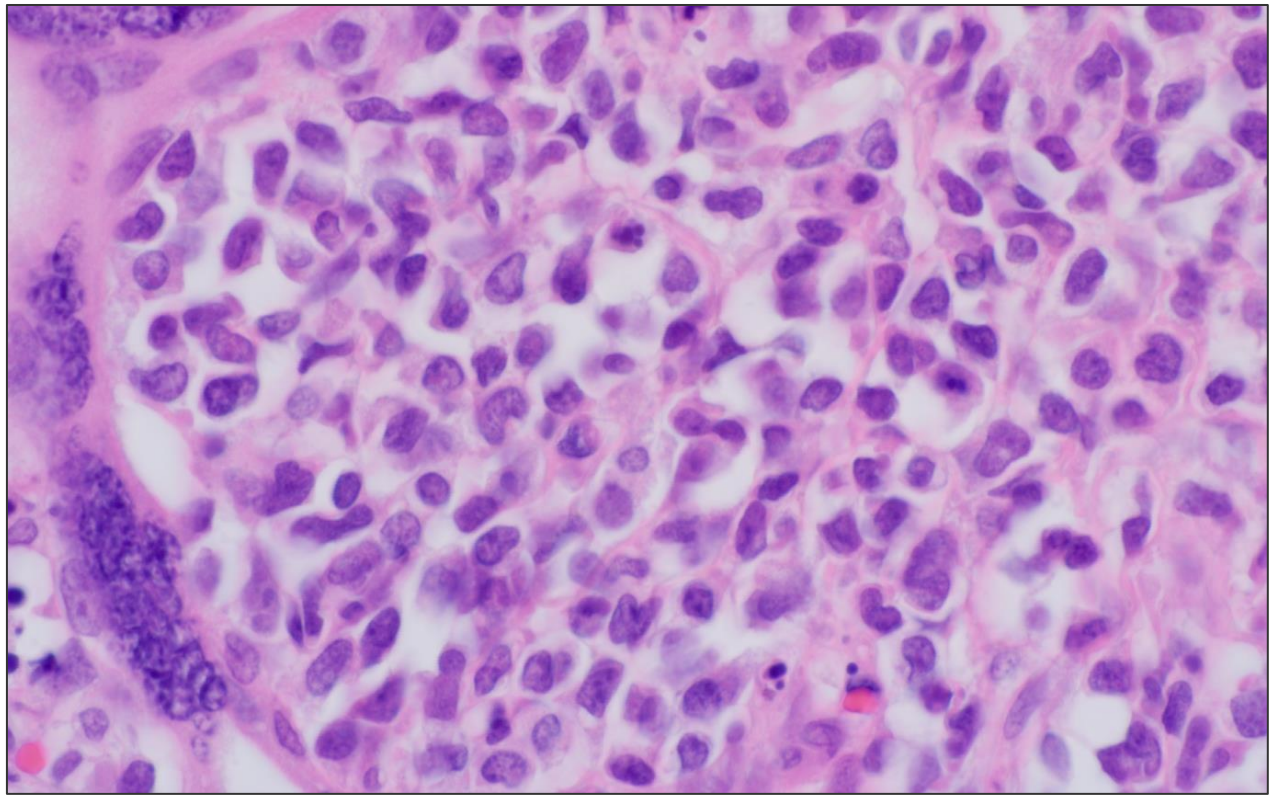
Blastic plasmacytoid DC neoplasm

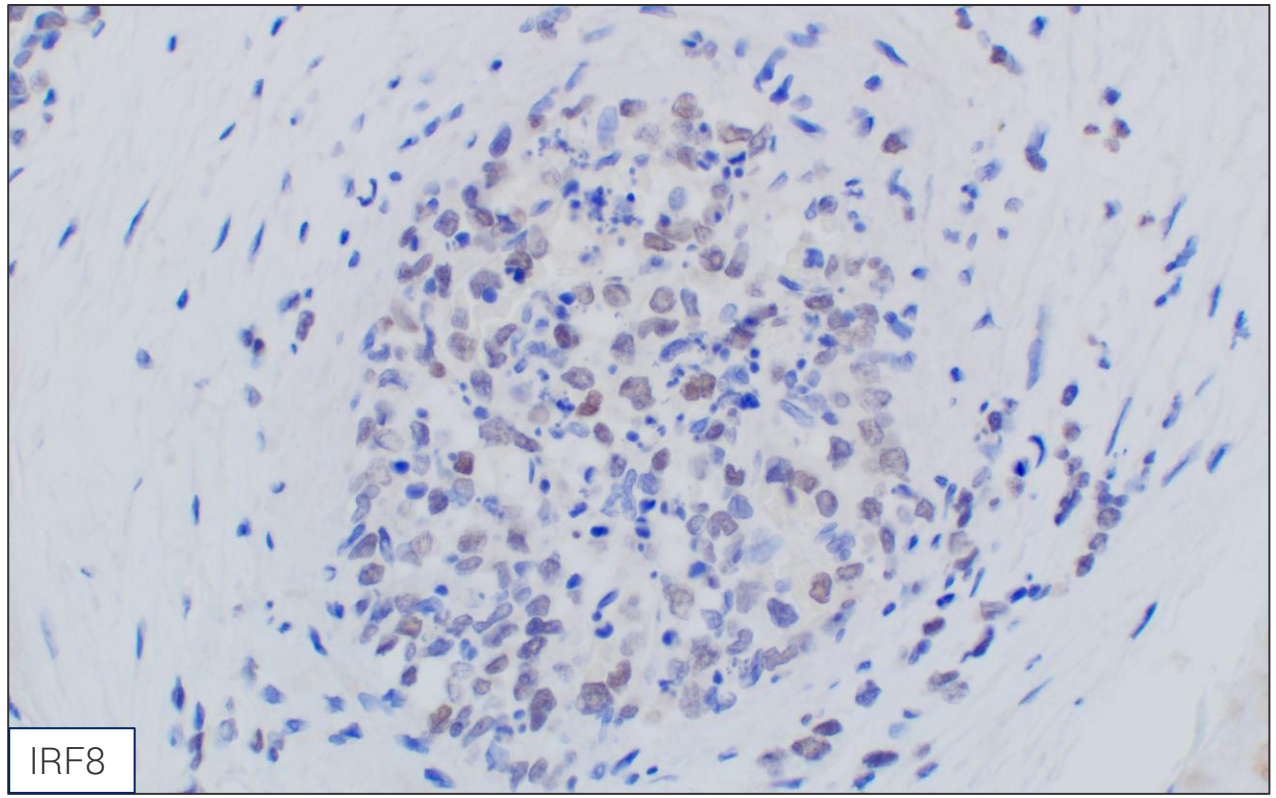


Histiocytic sarcoma



PATIENT 3





Diagnosis: Congenital AML with monocytic differentiation

Take home points

- IHC is a powerful diagnostic tool, but it should be used in morphologic context.
- Lack of standardization is IHC is more recognized. More markers will likely have “best practice” recommendations soon.
- Sometimes reintroducing “old friend” IHC stains can be beneficial.

Thank you