Multi-Institutional Hematopathology Interesting Case Conference

Avi Kandel, MD

Hematopathology Fellow

Icahn School of Medicine at Mount Sinai Hospital

3/19/2025

Mount Sinai

Clinical History

68-year-old male presented with skin lesions

Past Medical History

- 50 pack-year smoking history, thoracic aortic aneurysm, chronic kidney disease stage 3

Family history:

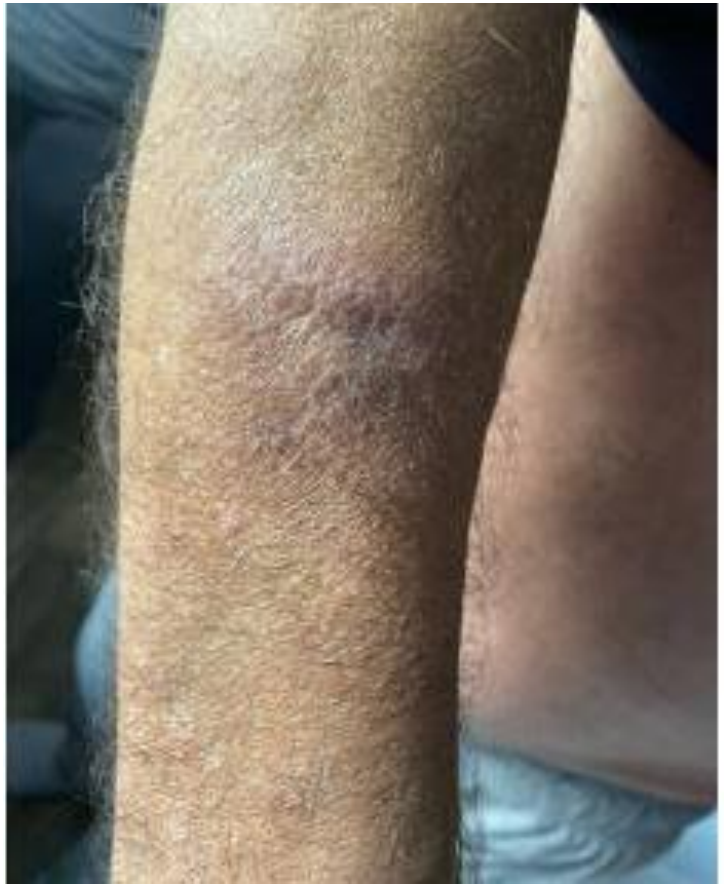
- Father - passed away from leukemia in 1975.
- Brother - treated for leukemia.

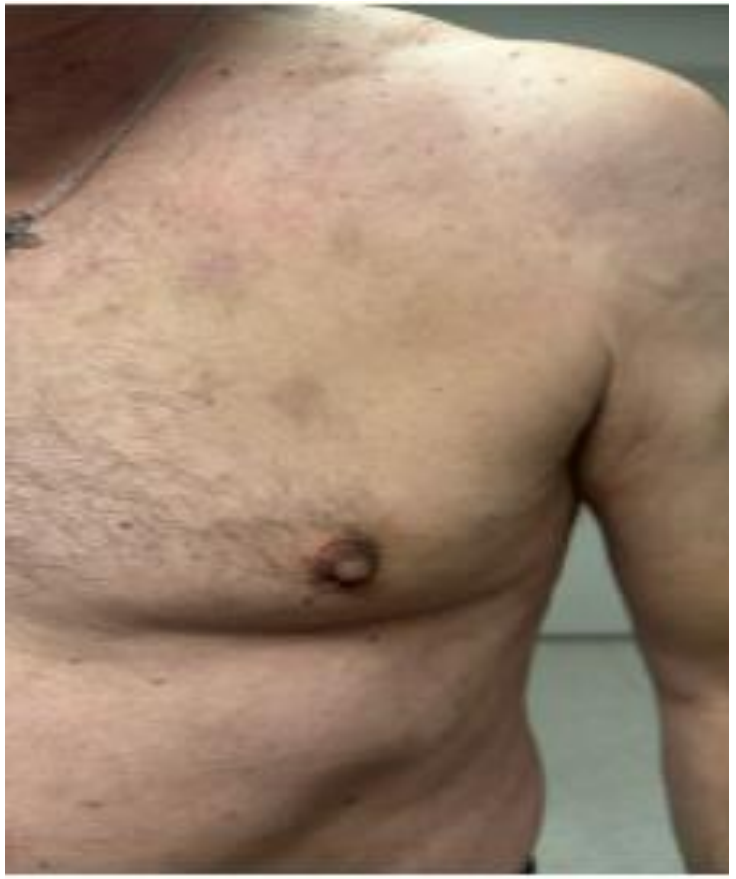
Physical Exam:

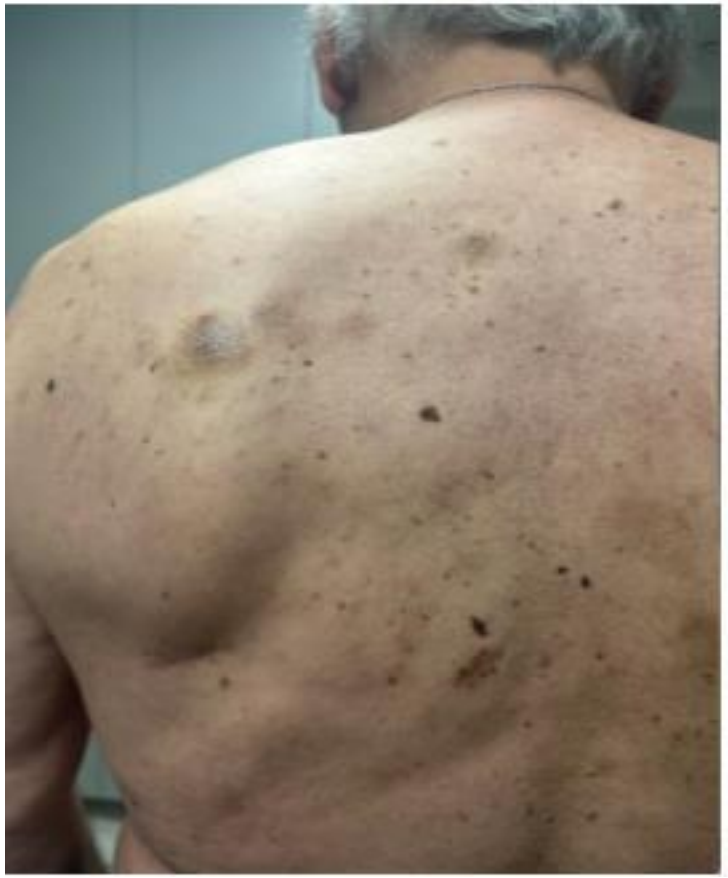
- Violaceous-pink raised painless skin lesions - Upper extremities and torso with an intermittent burning sensation
- No palpable adenopathy
- No palpable hepatosplenomegaly

Underwent skin punch biopsy of right distal forearm

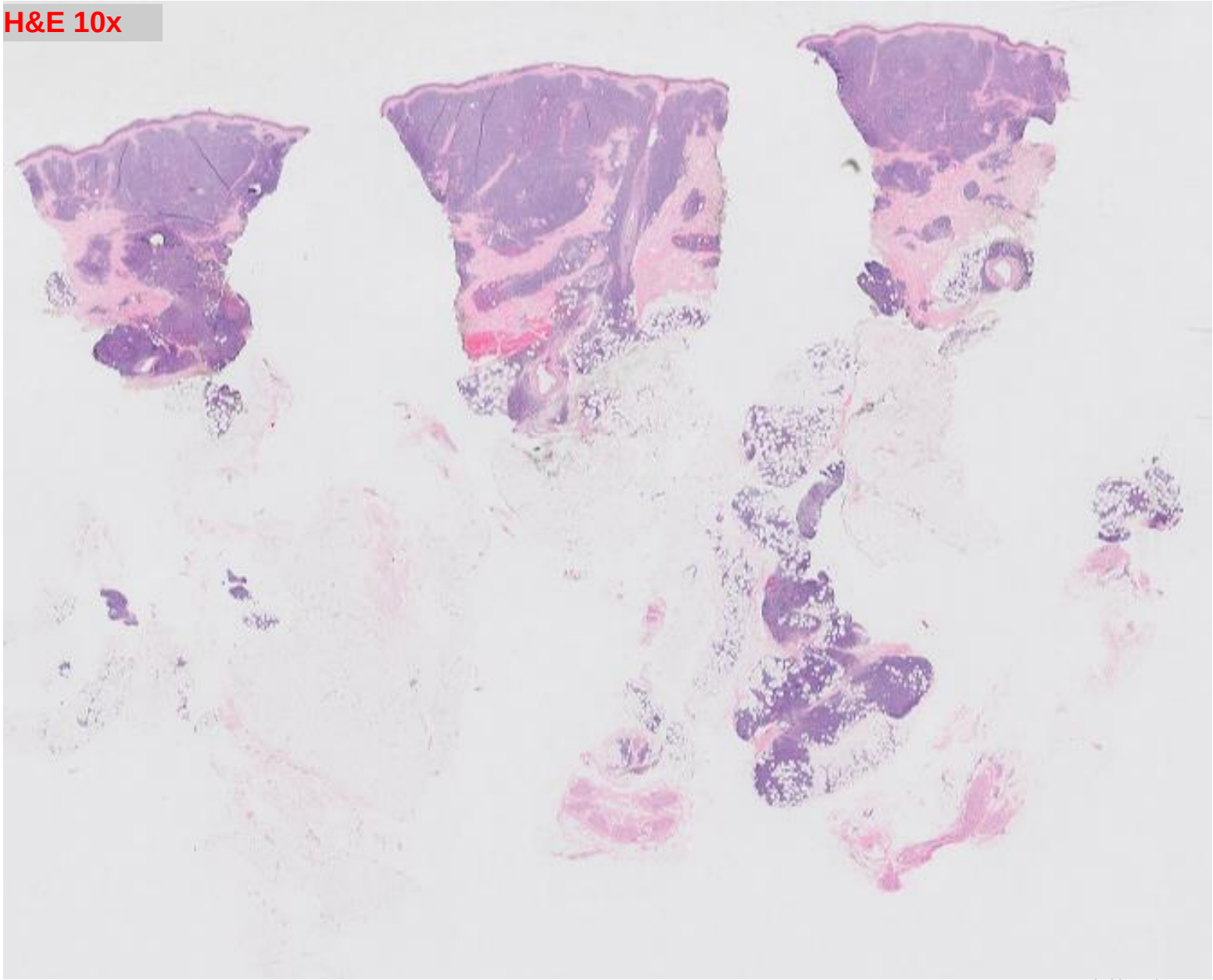
Clinical Photos



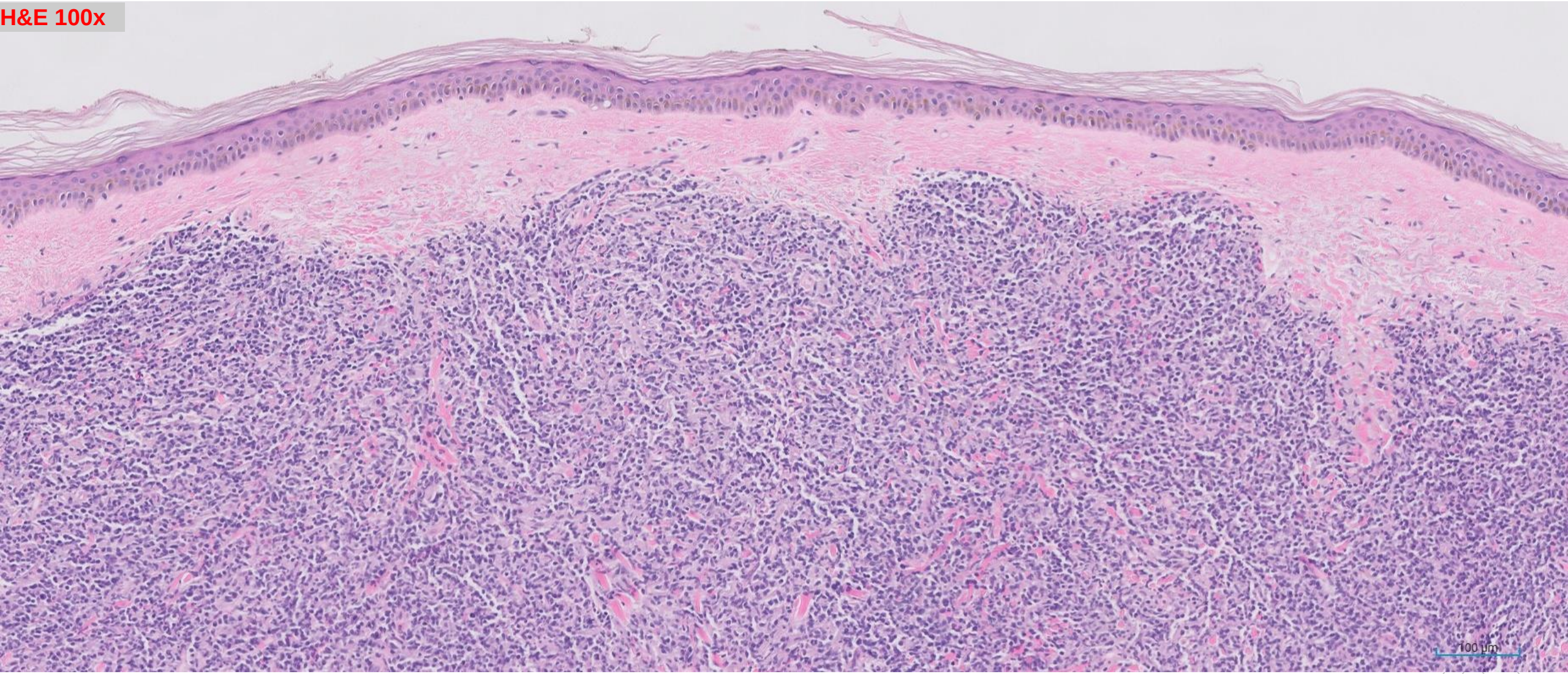




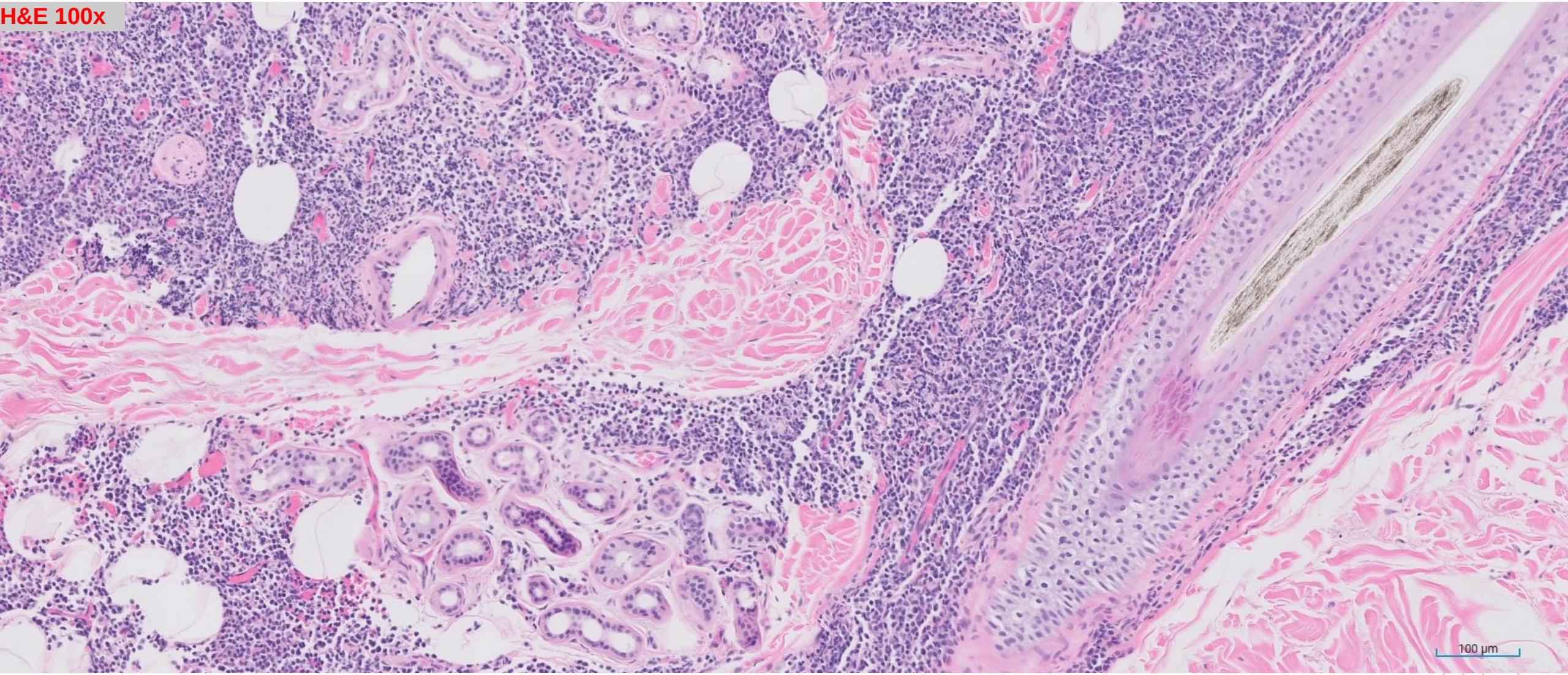
Skin Punch Biopsy



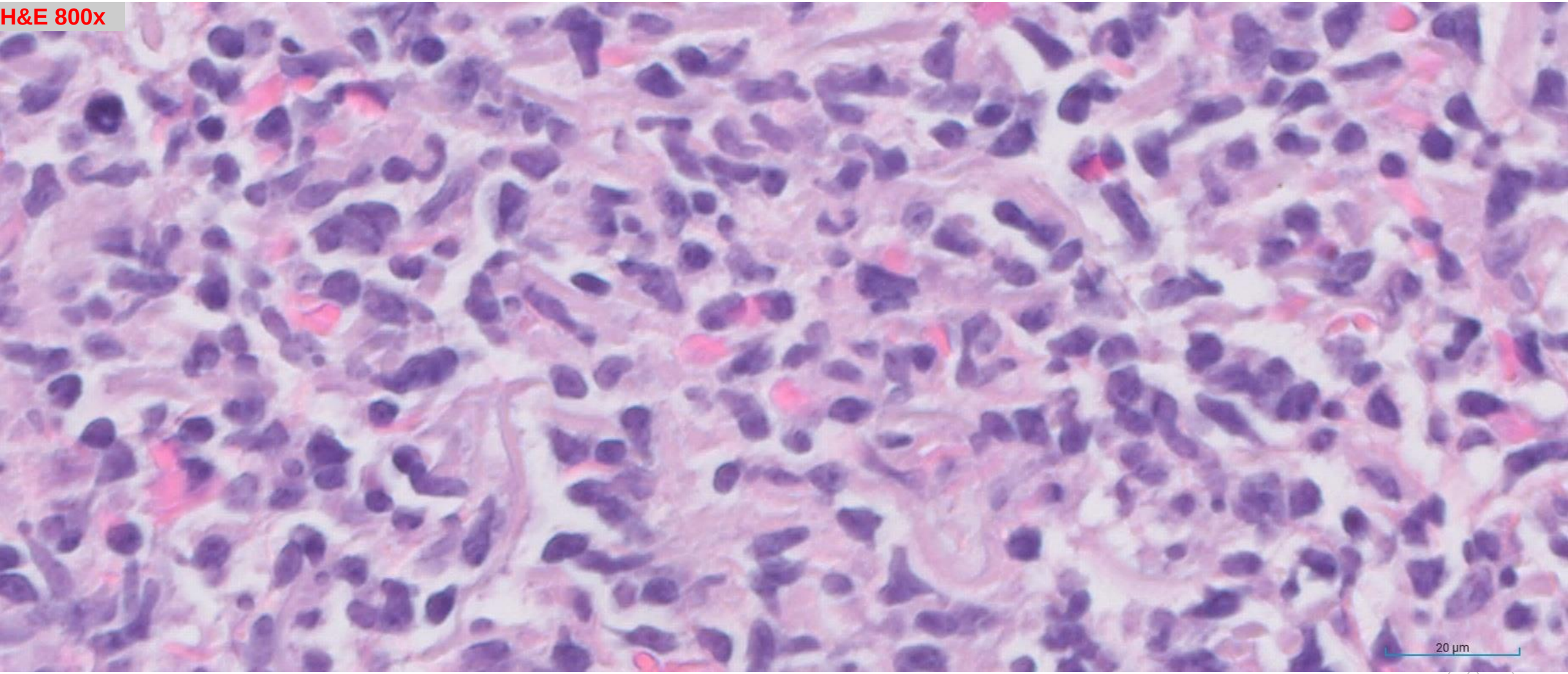
Skin Punch Biopsy



Skin Punch Biopsy

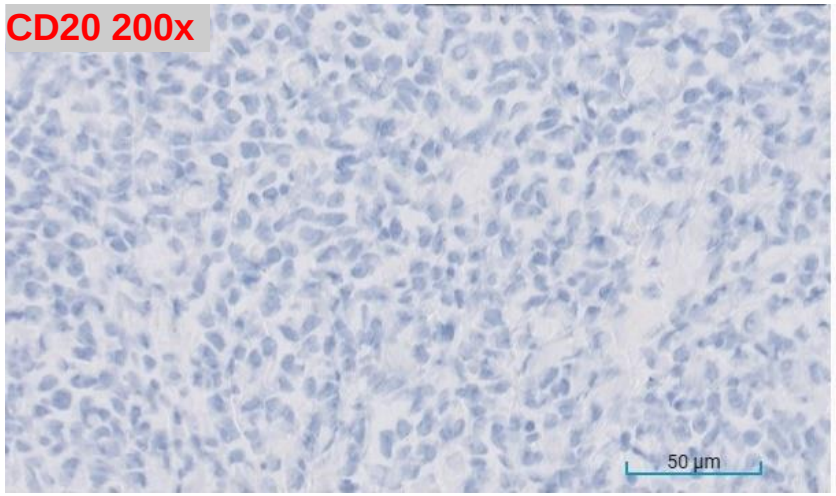


Skin Punch Biopsy

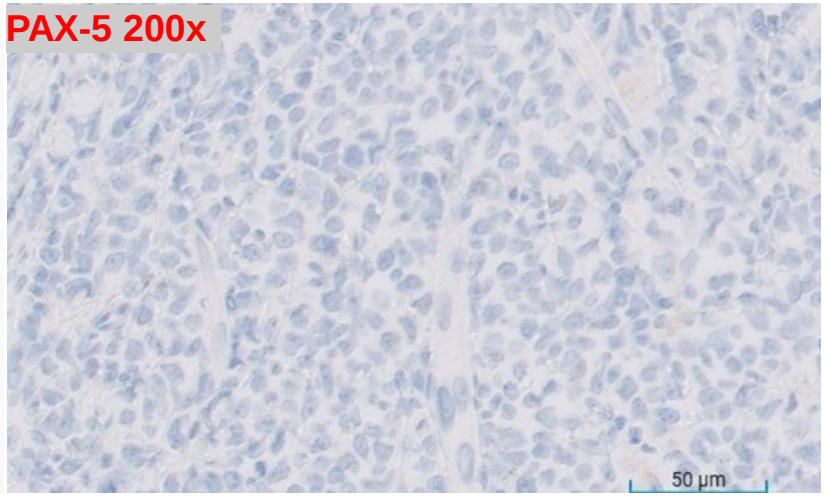


Skin Punch Biopsy

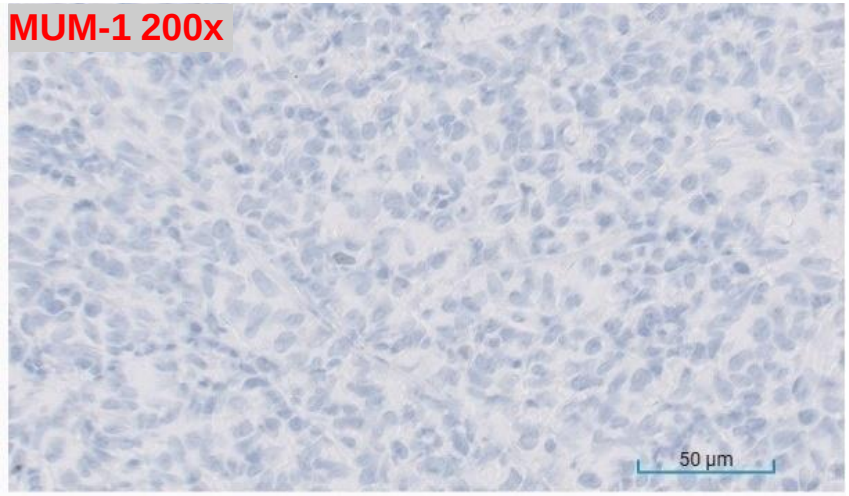
CD20 200x



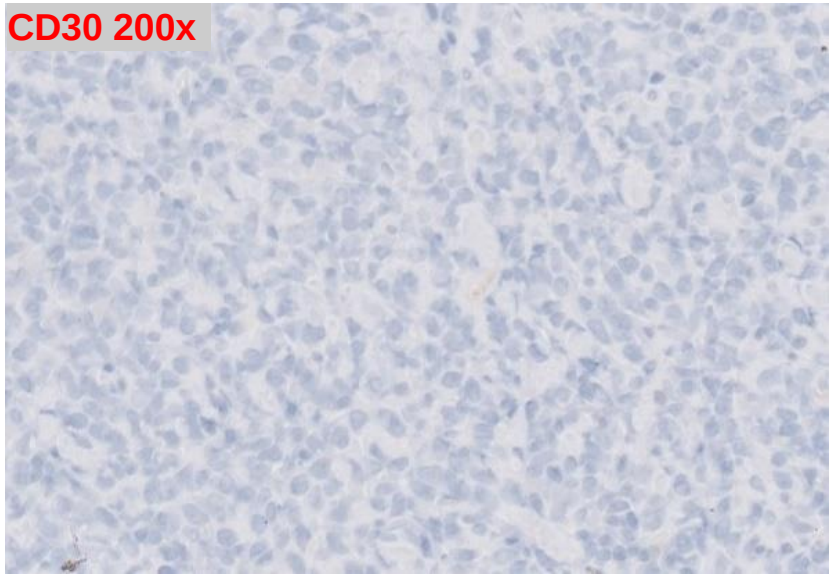
PAX-5 200x



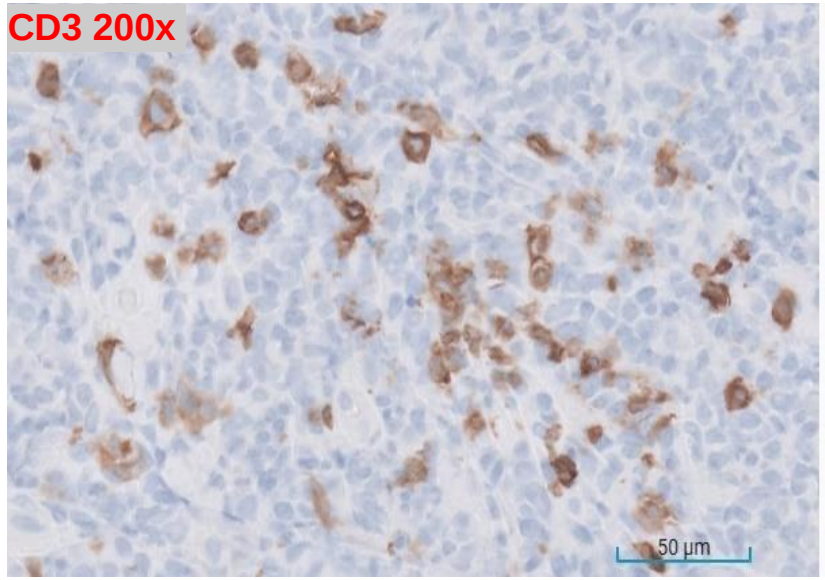
MUM-1 200x



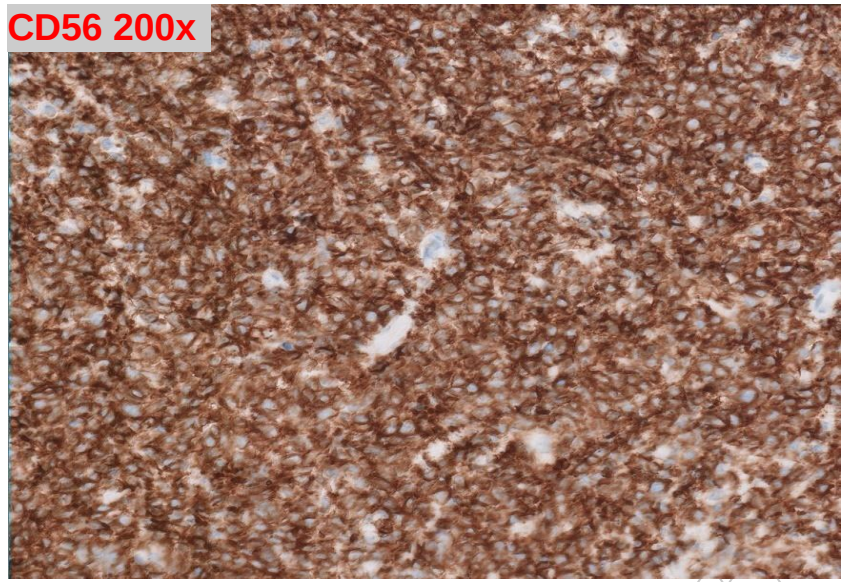
CD30 200x



CD3 200x



CD56 200x



Differential Diagnosis?

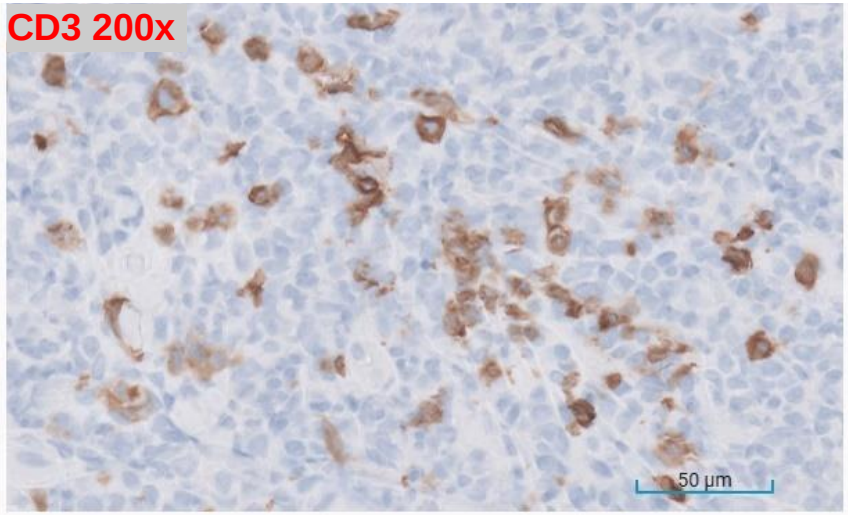
NK/T cell lymphoma

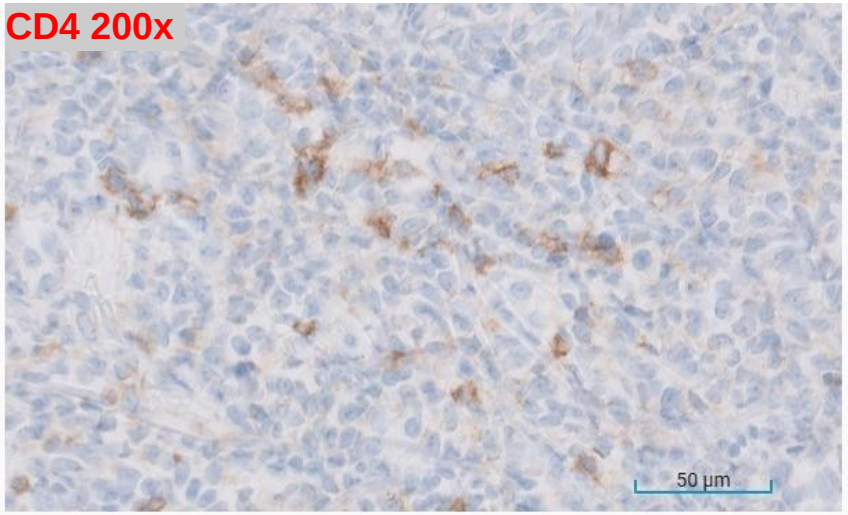
Leukemia cutis

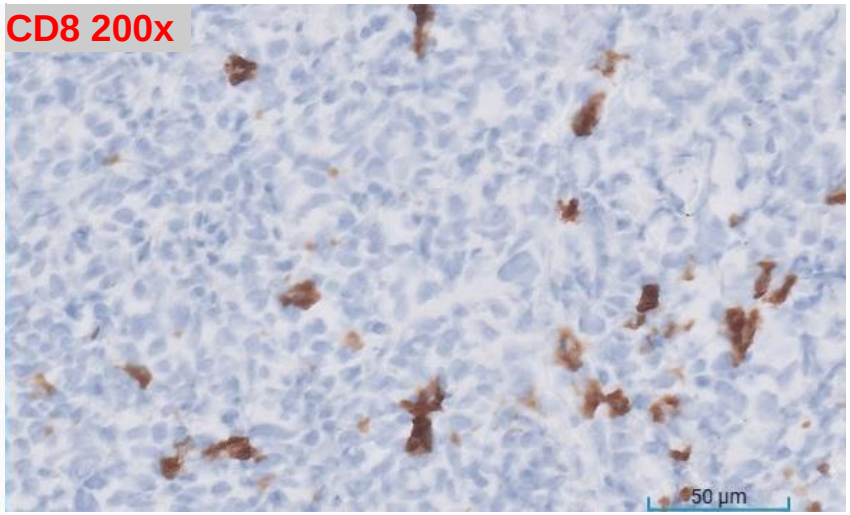
Histiocytic sarcoma

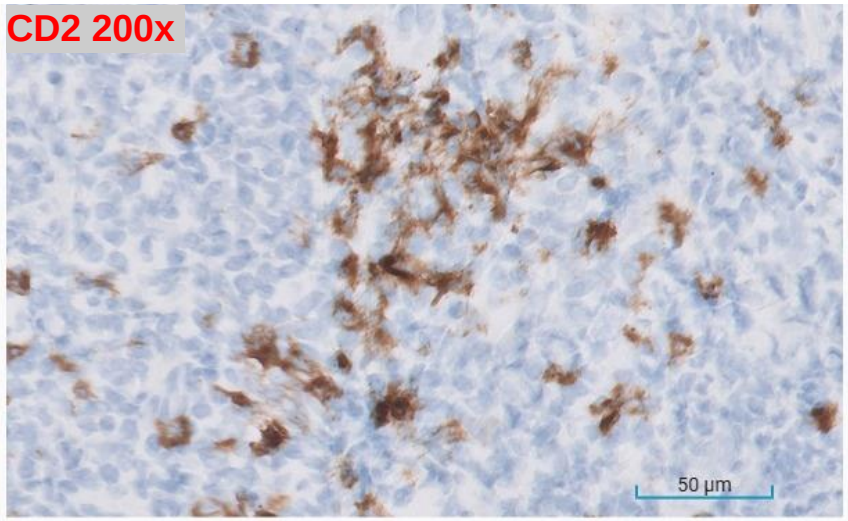
Blastic plasmacytoid dendritic cell neoplasm

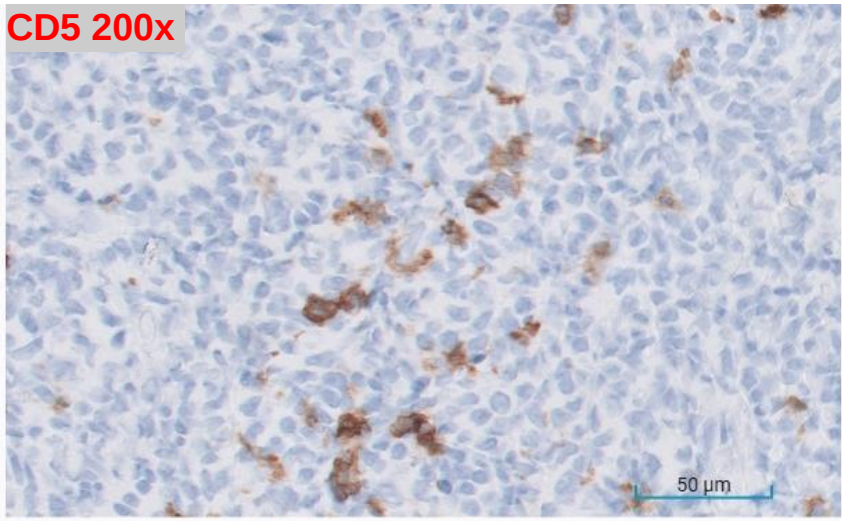
Skin Punch Biopsy

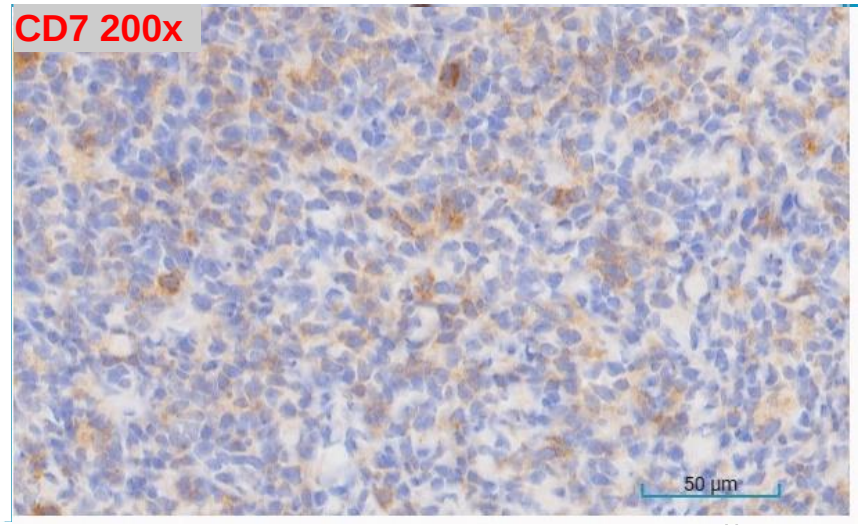




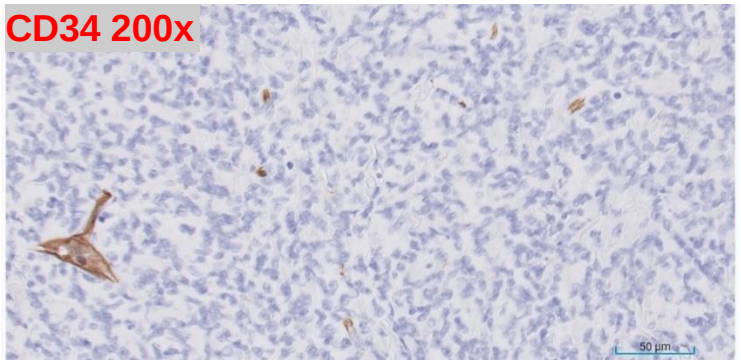


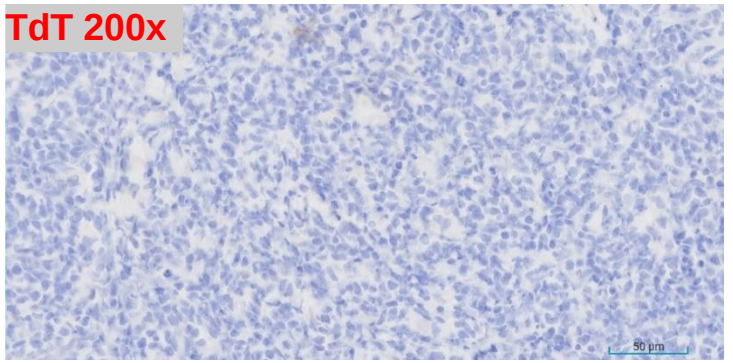


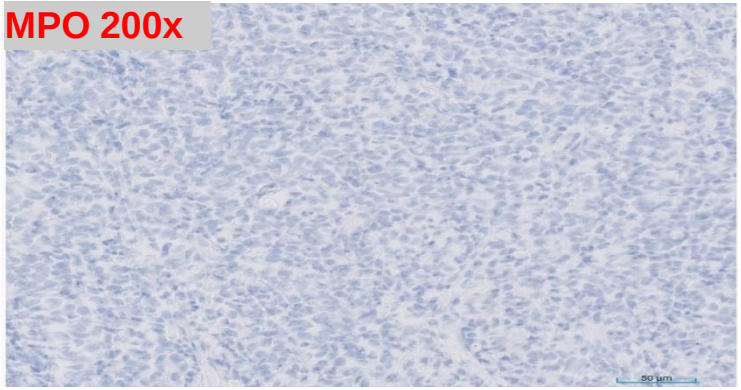


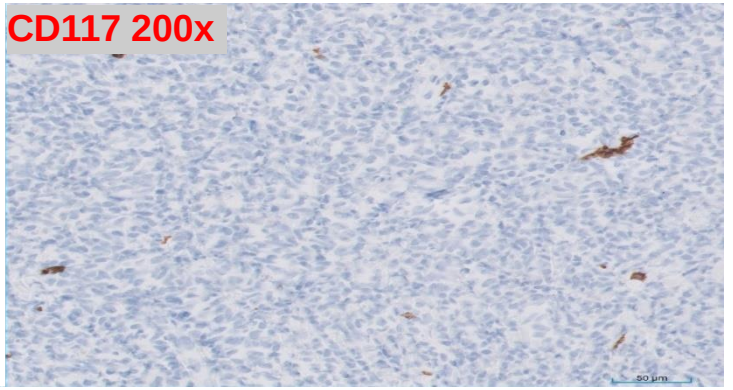


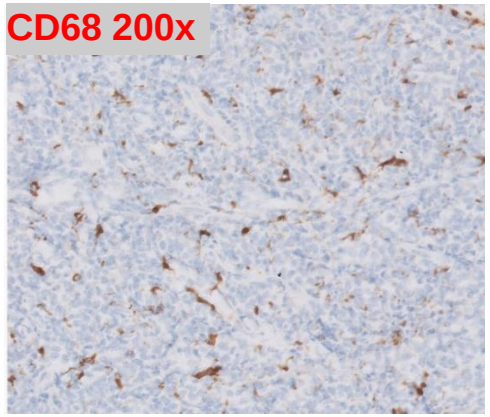
Skin Punch Biopsy

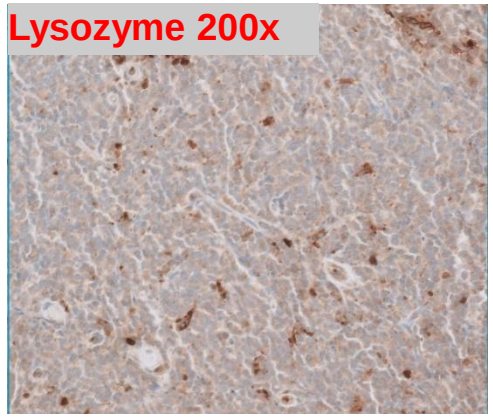


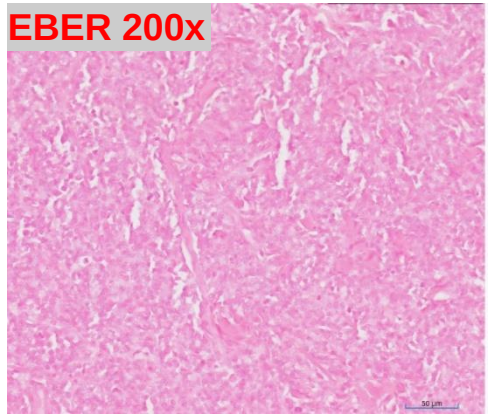






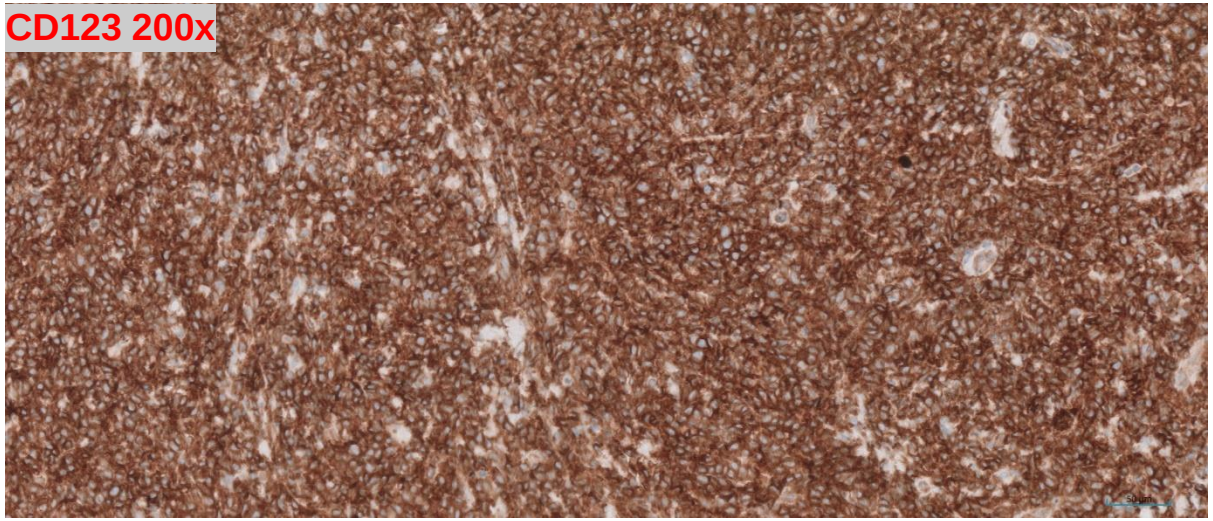




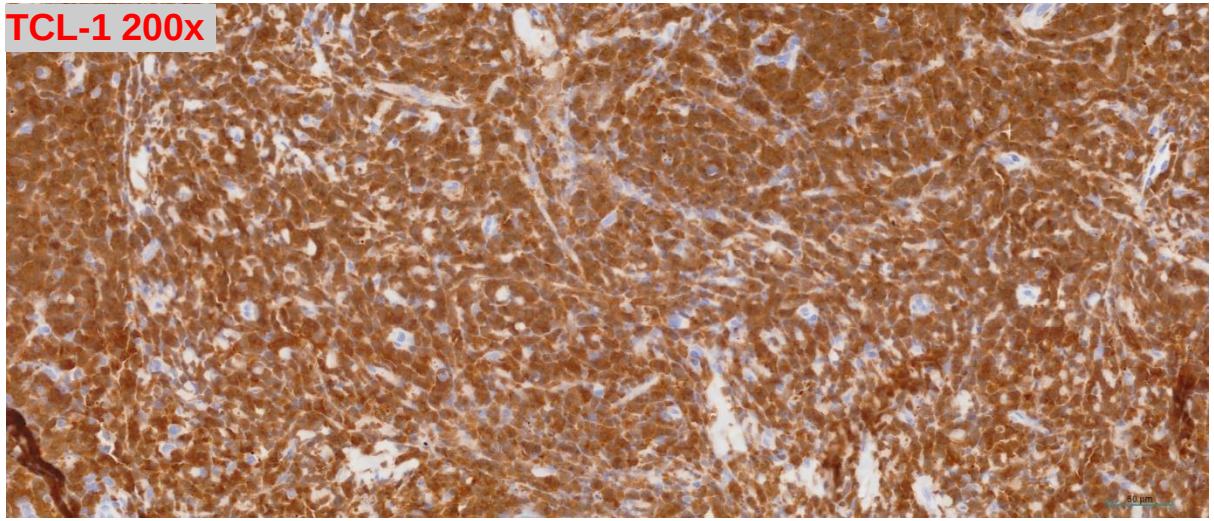


Skin Punch Biopsy

CD123 200x



TCL-1 200x



Summary of Immunohistochemistry Results

Markers		Results
Immaturity	CD34	Negative
	TDT	Negative
B cell and plasma cells	CD20	Negative
	PAX5	Negative
	MUM1	Negative
T cell	CD2	Negative
	CD3	Negative
	CD4	Negative
	CD5	Negative
	CD7	Partial weak
	CD8	Negative
NK cell	CD56	STRONG
Myeloid	MPO	Negative
	Lysozyme	Negative
Monocytic	CD68	Negative
Dendritic	CD123	STRONG
	TCL1	STRONG
	EBER	Negative

Skin Punch Biopsy

DIAGNOSIS:

RIGHT DISTAL FOREARM, PUNCH BIOPSY-

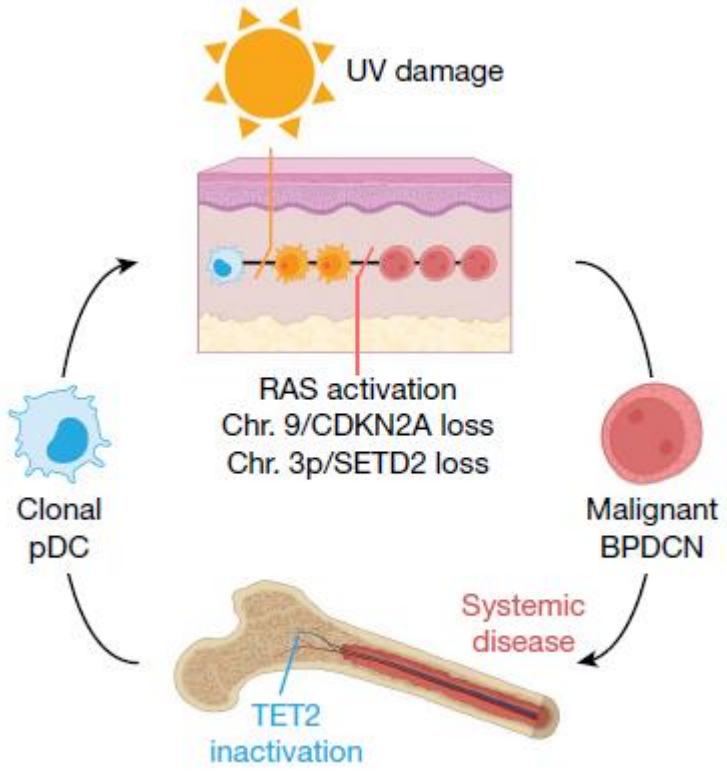
- BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM

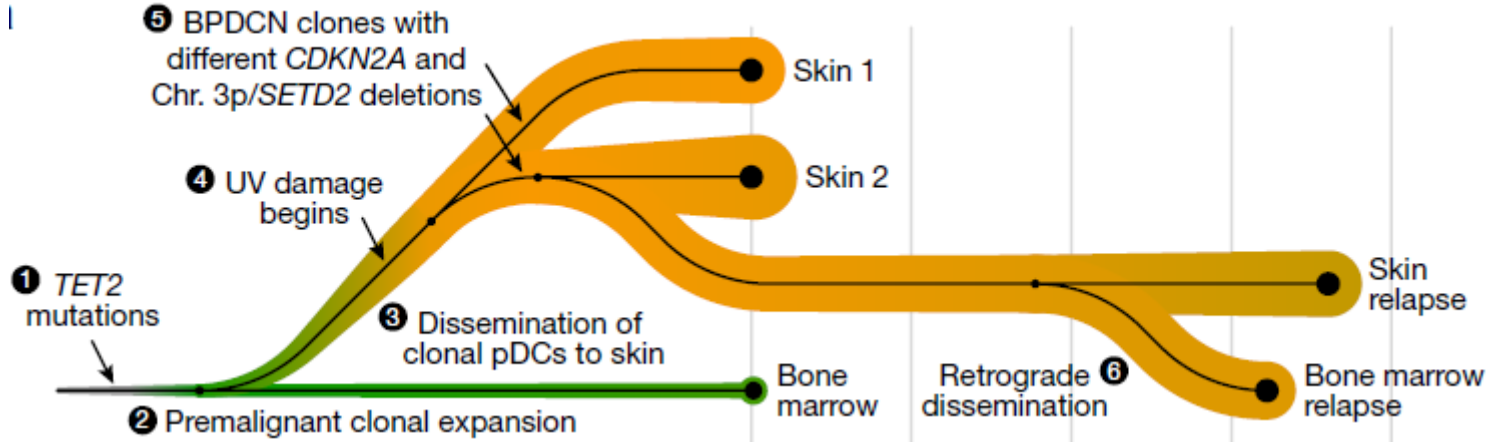
Blastic plasmacytoid dendritic cell neoplasm

- Consists of immature cells with plasmacytoid dendritic cell (pDC) differentiation
- pDCs
  - Secrete interferon and act as antigen presenters
- Clinical features
  - Median age ~67 years
  - Male dominance
  - Skin lesions varying in size and color
- Genetic features
  - Proliferation and hematopoietic differentiation (*ETV6* loss) (Tang, Zhenya, et al. *Leukemia Research* 2018)
  - Epigenetic regulation (*TET2* and *ASXL1*) (Menezes J, et al. *Leukemia* 2014)
  - RNA splicing (e.g. *SRSF2*) (Brunetti et al, *Leukemia*. 2017)

UV Radiation and BPDCN

One study found that plasmacytoid dendritic cells derived from clonal BM progenitors seed the skin and subsequently transform to BPDCN in association with UV damage in sun-exposed sites (Griffin et al. *Nature*. 2023)





Diagnostic criteria for blastic plasmacytoid dendritic cell neoplasm

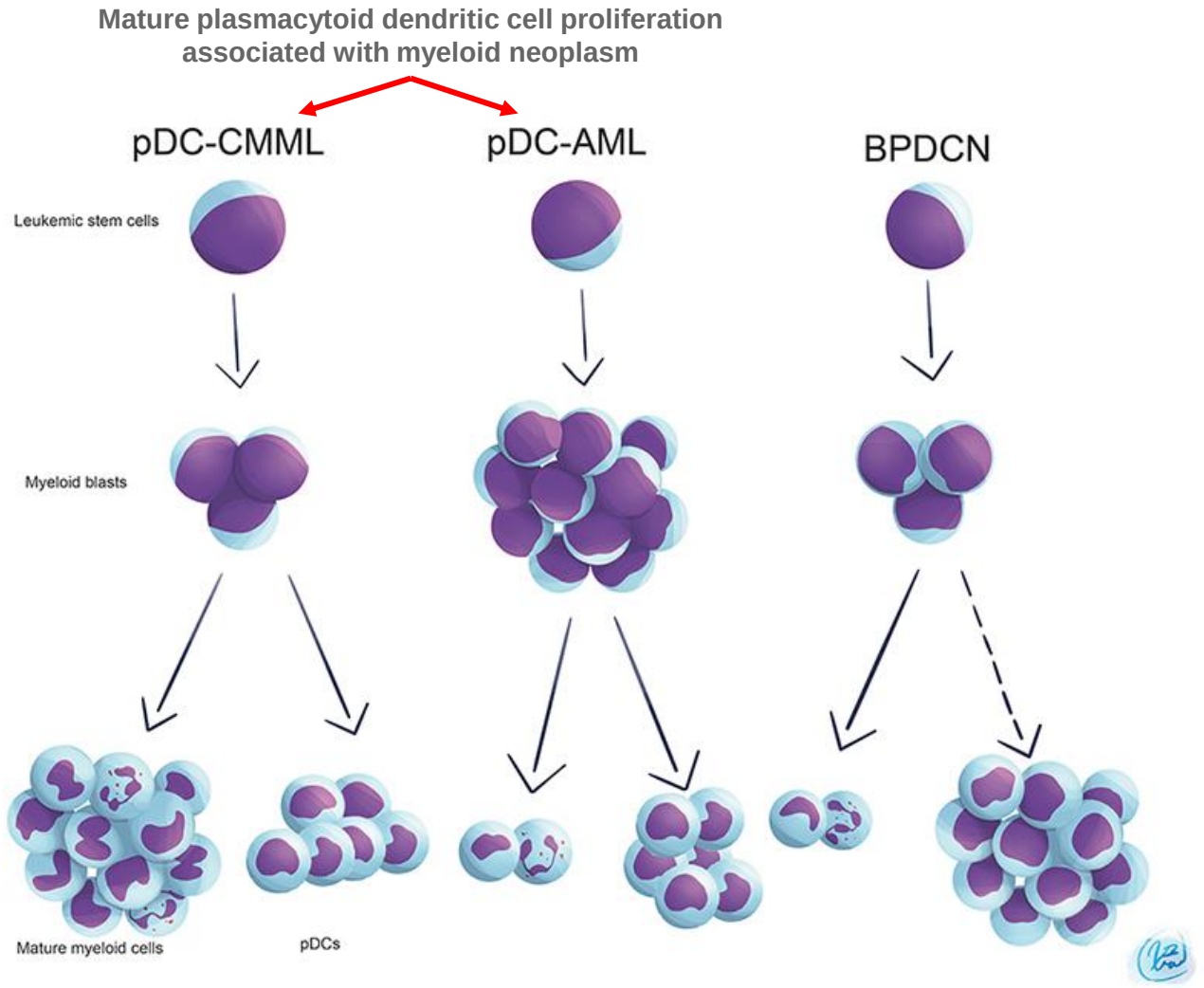
World Health Organization 5th edition	
Expected positive markers	
pDC markers:	
	CD123
	TCF4
	TCL1
	CD303
	CD304
Other markers:	
	CD4
	CD56
Expected negative markers	
	CD3
	CD14
	CD19
	CD34
	Lysozyme
	Myeloperoxidase
Immunophenotypic diagnostic criteria	
	Expression of CD123 and one other pDC marker in addition to CD4 and/or CD56
	OR
	Expression of any three pDC markers and absent expression of all expected negative markers

International Consensus Classification 2022	
At least two of the following expressed	
TCF4, CD123, CD303, TCL1, CD304	
Also typically expressed	
	CD4
	CD56
Exclusionary markers	
	CD3
	CD19
	CD20
	CD14
	Lysozyme
	Myeloperoxidase
	CD34

Khoury JD, Takeuchi K, Gru A, Ottou FG. Blastic plasmacytoid dendritic cell neoplasm. In: WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. Lyon (France): International Agency for Research on Cancer; 2024. (WHO classification of tumours series, 5th ed.; vol. 11). https://publications.iarc.who.int/637.

Arber, Daniel A., et al. "International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data." *Blood, The Journal of the American Society of Hematology* 140.11 (2022): 1200-1228.

Other proliferations of pDCs



RAS pathway mutations

RUNX1 mutations

Wenbin Xiao et al. *Blood* 2021

Differentiating BPDCN from mature pDCs and pDC-AML

	BPDCN	Mature pDC Associated with CMML	pDC-AML
CD123	+	+	+
CD56	+	+/-	-
CD4	+	+	+
TCL1	+	+/-	-
TCF4	+	+	+
CD303	+/-	+/-	+
CD68	-	+	
Granzyme B	-	+	
BCL2	+	-	
CD117	+/-	-	+/-
CD33	+/-	+/-	+/-
CD13	+/-	+/-	+/-
MPO	-	-	-
sCD3	-	-	-
CD5	+/-	-	+/-
CD7	+/-	-	+/-
TdT	+/-	+/-	+/-
CD34	-	+/-	+

Wang, Wei, et al, *Cancers* (2022)

Vitte, Franck, et al. *The American Journal of Surgical Pathology* (2012)

CD4-negative BPDCN

AJCP / Original Article

CD4-Negative Variant of Cutaneous Blastic Plasmacytoid Dendritic Cell Neoplasm With a Novel *PBRM1* Mutation in an 11-Year-Old Girl

Nuri Yigit, MD,[1,3] Luisa Fernanda Suarez,[1] Lisa Giulino Roth, MD,[2] Attilio Orazi, MD,[1] and Wayne Tam, MD, PhD[1]

From the [1]Division of Hematopathology, Department of Pathology and Laboratory Medicine, and [2]Department of Pediatrics, Weill Cornell Medical College, New York, NY; and [3]Department of Pathology, Gulhane Military Medical Academy and School of Medicine, Kecioren, Ankara, Turkey.

Yao, Xiaosai, and Bin Tean Teh. *NATURE CELL BIOLOGY* (2023)

PBRM1 identified as driver mutation

TET2 and *ASXL1* were not detected

Emphasizes the need for using a robust panel of IHC for BPDCNs

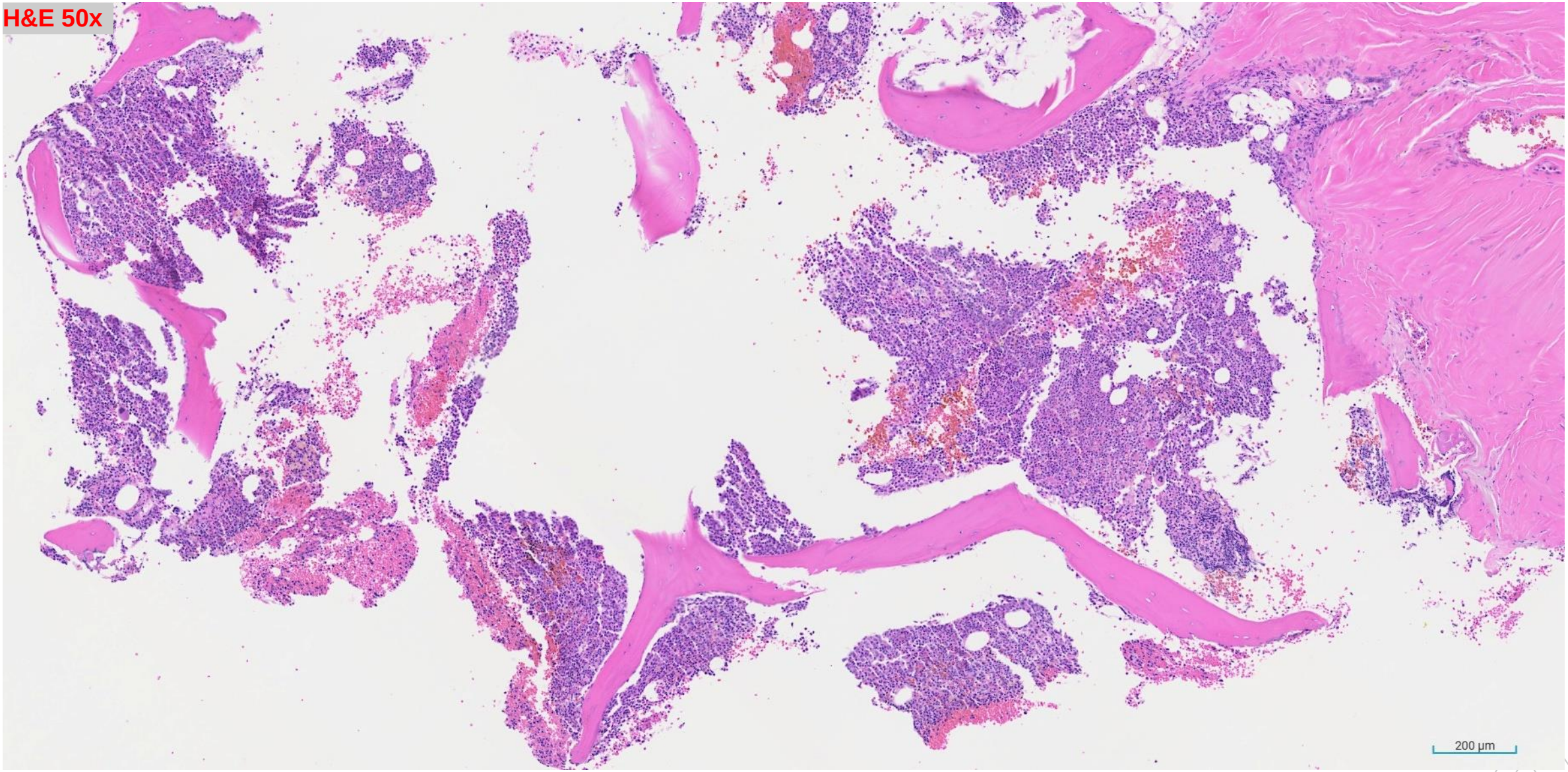
Clinical History

9 weeks after skin biopsy underwent bone marrow biopsy

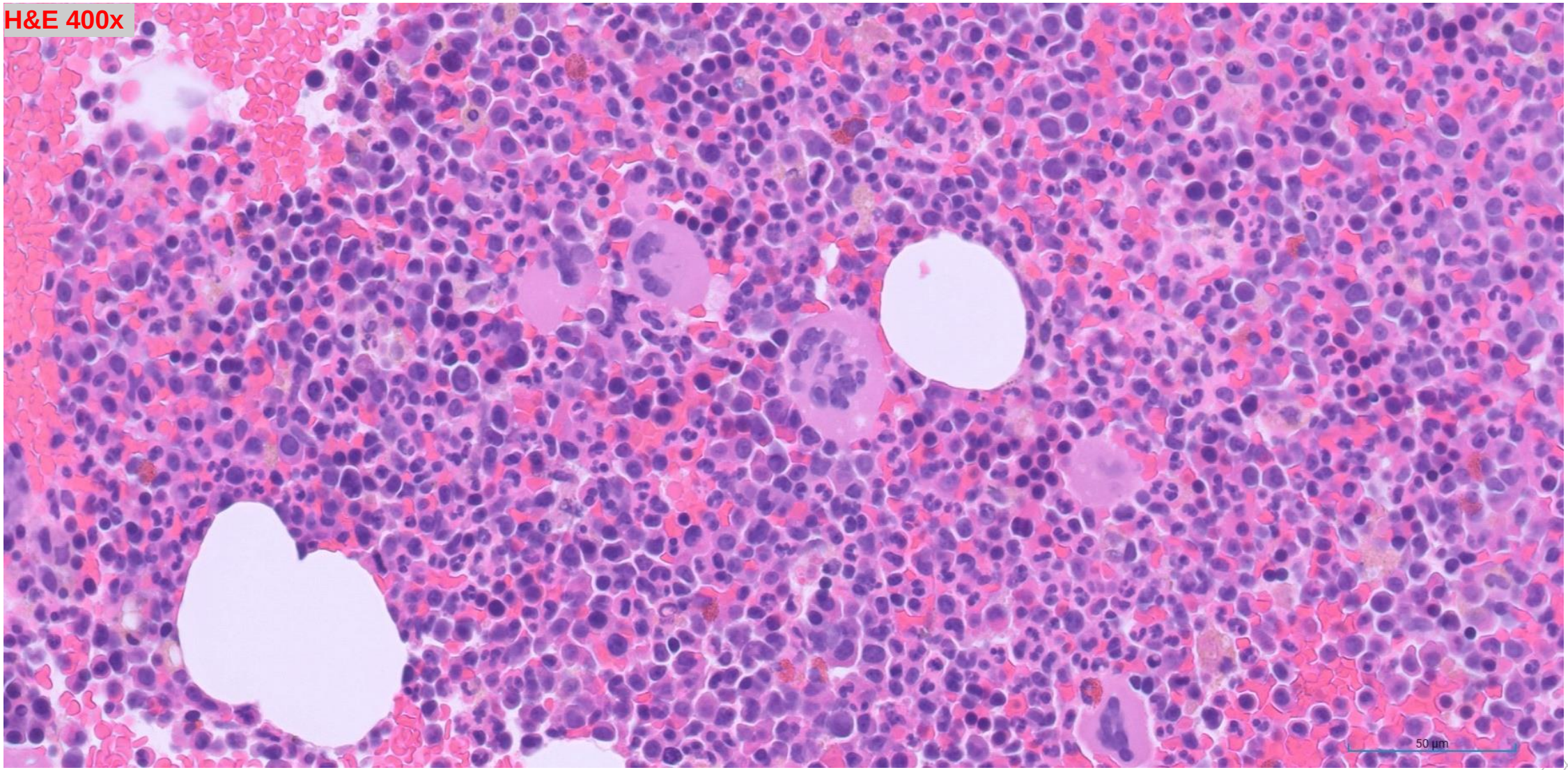
PET/CT with hypermetabolic activity of the bone

Neutrophil	31.8%
Lymphocyte	47.3%
Monocyte	15.4%
Eosinophils	3.8%
ABS Neutrophil	1.4 K/uL
ABS Monocyte	0.7 K/uL

Bone marrow biopsy

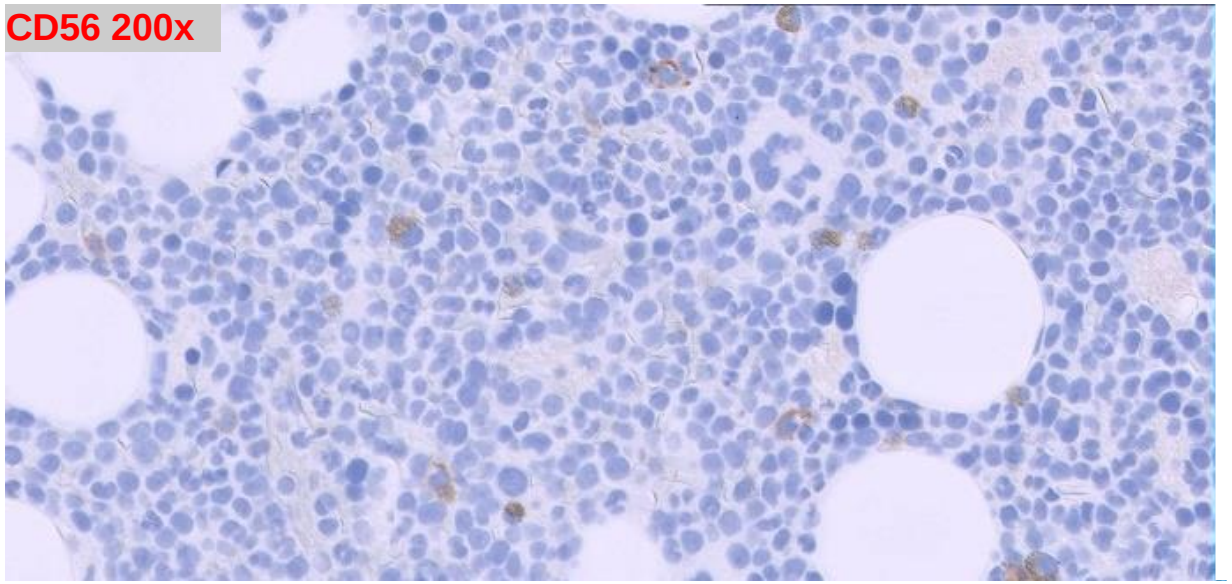


Bone marrow biopsy

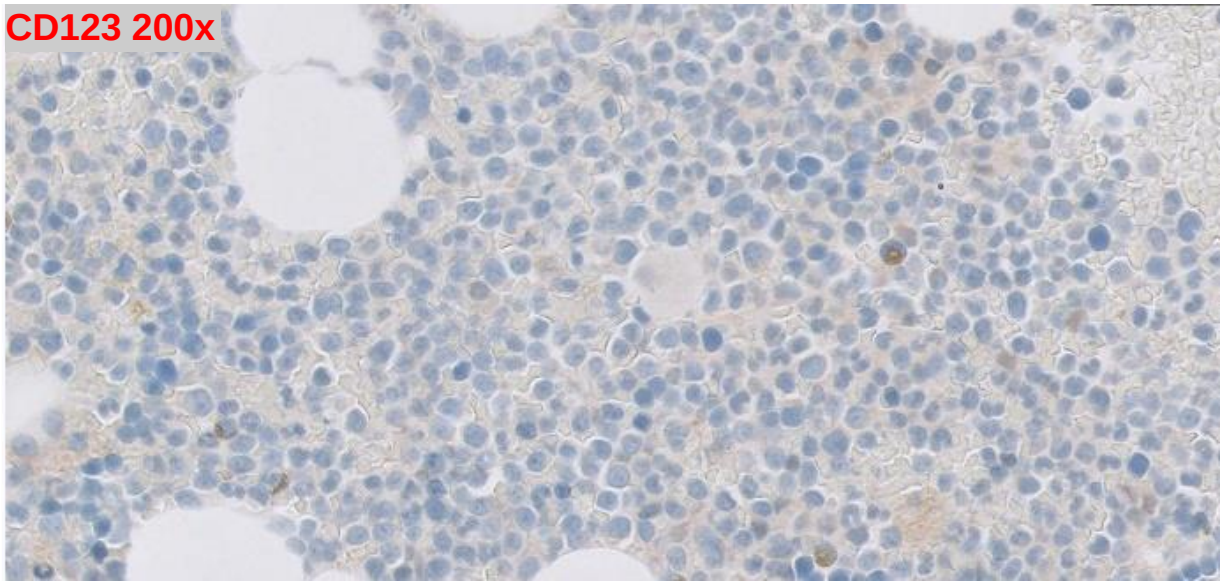


Bone marrow biopsy

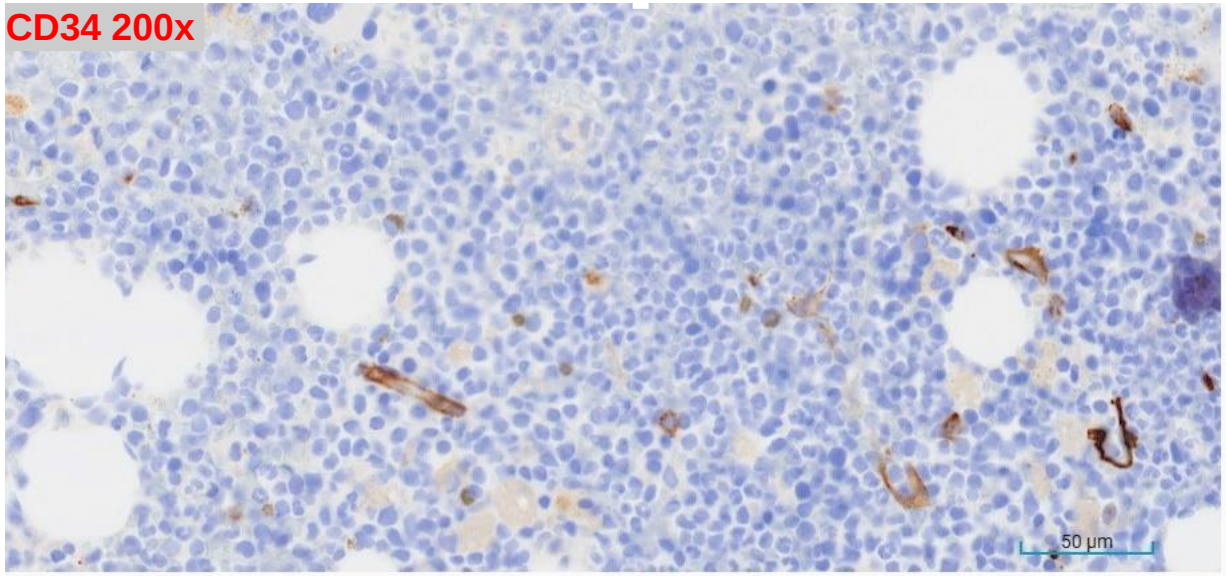
CD56 200x



CD123 200x



CD34 200x



Cytogenetic Studies

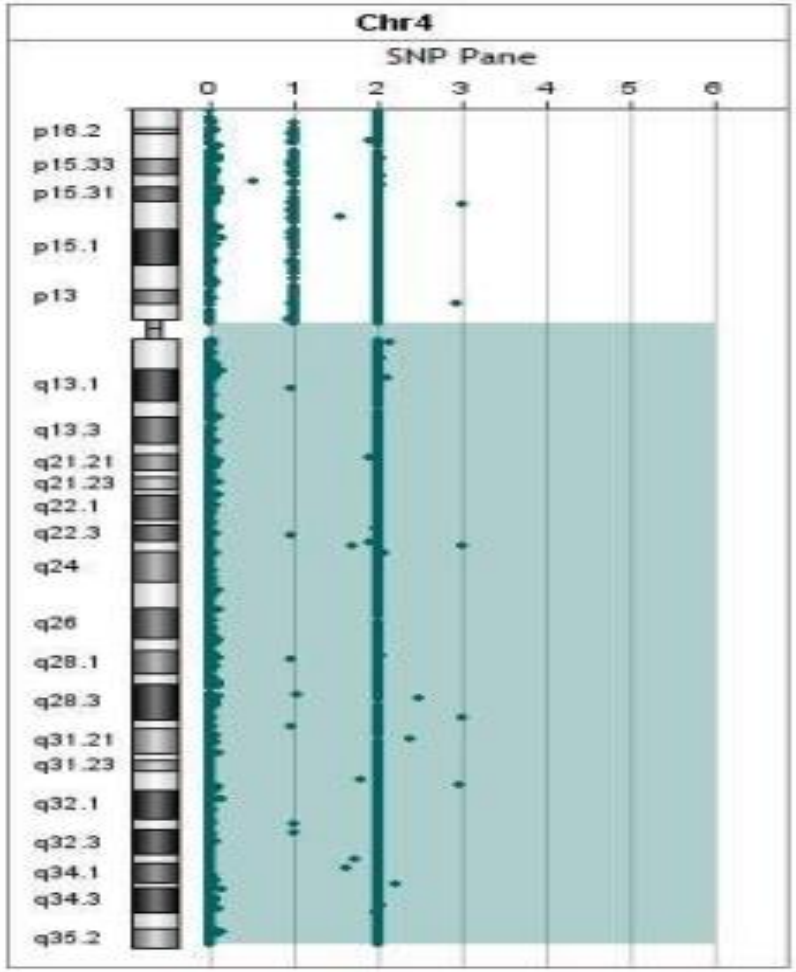
46, XY [20]

FISH Panel Normal

FISH probes tested
KMT2A(ba)
CFB ba
RUNX1T1-RUNX1 DF
BCR-ABL ES
PML-RARA DF
CEP8-D8Z2
MYC ba
TP53/D17Z1

Microarray

Chr	Cytoband	Size (kb)	Genomic Status	Gene
4	p11 – q35.2	141,543	LOH	*TET2*



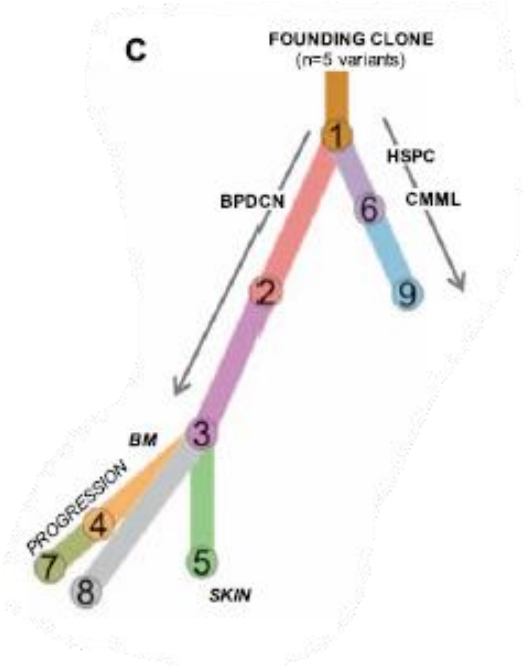
Bone Marrow NGS Studies

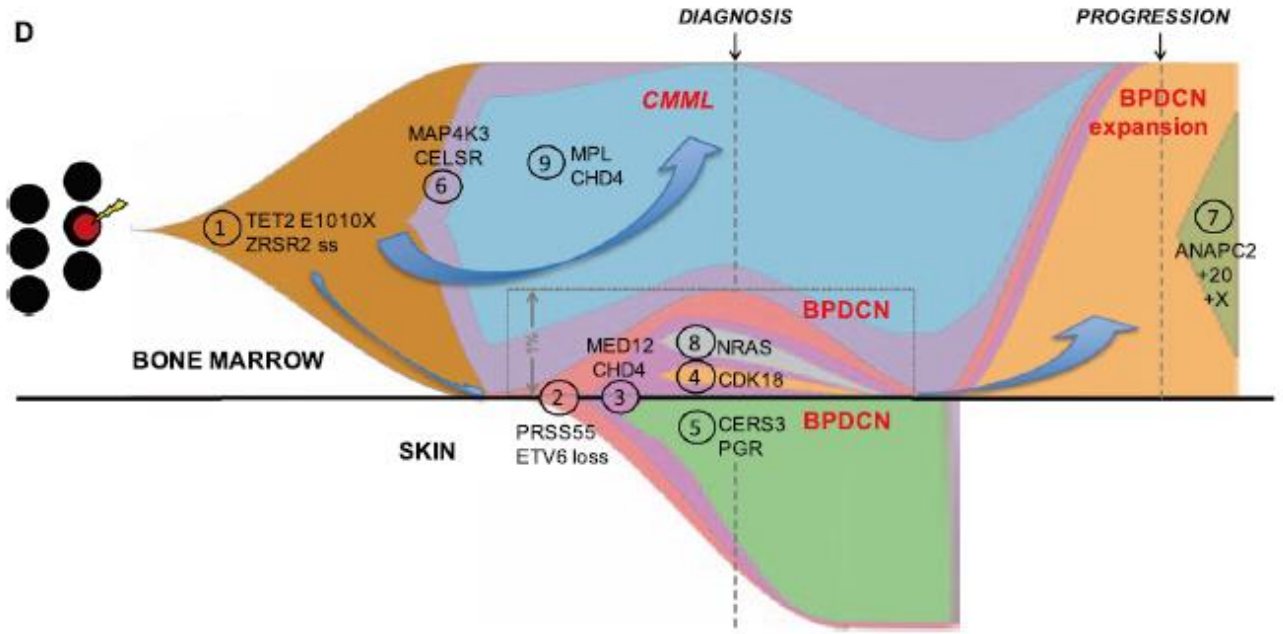
Gene	Mutation	VAF
ASXL1	P.Q803*	48%
SRSF2	p.P95L	54.3%
TET2	SPLICE SITE c.3954+1G>T	95.7%

Bone marrow biopsy

DIAGNOSIS:
- Consistent with chronic myelomonocytic leukemia

BPDCN co-occurrence with CMML, shared mutations





- BPDCN and CMML - shared clonal *TET2* mutations in several studies.
- Other shared mutations-

  SRSF2 (Brunetti et al, *Leukemia*. 2017, *Patnaik et al. Blood Cancer J. 2018*)

Batta K, Bossenbroek HM, et al.. Leukemia. 2021

Conclusion

- CD4 negative BPDCN may potentially be a distinct entity.
- A robust panel of immunohistochemistry is useful to differentiate BPDCN from other pDC proliferations
- BPDCNs and CMML share common mutations and support a clonal relationship.

Thank you

Hematopathology
Amy Duffield
Shafinaz Hussein
Alina Dulau
Bruce Petersen
Christian Salib
Dalia Azim
Matthew Shapiro

Cytogenomics Laboratory
Vesna Najfeld
Joseph Tripodi

Dermatopathology
Robert Phelps
George Niedt
Avi Bitterman

Mount Sinai

References

Kanagal-Shamanna, Rashmi, et al. "Assessing copy number aberrations and copy neutral loss of heterozygosity across the genome as best practice: An evidence based review of clinical utility from the cancer genomics consortium (CGC) working group for myelodysplastic syndrome, myelodysplastic/myeloproliferative and myeloproliferative neoplasms." *Cancer genetics* 228 (2018): 197-217.

Menezes J, Acquadro F, Wiseman M, et al. Exome sequencing reveals novel and recurrent mutations with clinical impact in blastic plasmacytoid dendritic cell neoplasm. Leukemia. 2014;28:823-829.

Tang, Zhenya, et al. "Genomic aberrations involving 12p/ETV6 are highly prevalent in blastic plasmacytoid dendritic cell neoplasms and might represent early clonal events." *Leukemia Research* 73 (2018): 86-94.

Zhang, Xi, et al. "Biallelic TET2 mutations and canonical ASXL1 mutations are frequent and cooccur in Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN): An institutional experience and review of literature." *EJHaem* 4.1 (2023): 236-240.

Yigit, Nuri, et al. "CD4-negative variant of cutaneous blastic plasmacytoid dendritic cell neoplasm with a novel PBRM1 mutation in an 11-year-old girl." *American Journal of Clinical Pathology* 147.5 (2017): 453-460

Batta K, Bossenbroek HM, Pemmaraju N, Wilks DP, Chasty R, Dennis M, Milne P, Collin M, Beird HC, Taylor J, Patnaik MM, Cargo CA, Somervaille TCP, Wiseman DH. Divergent clonal evolution of blastic plasmacytoid dendritic cell neoplasm and chronic myelomonocytic leukemia from a shared TET2-mutated origin. Leukemia. 2021 Nov;35(11):3299-3303. doi: 10.1038/s41375-021-01228-y. Epub 2021 Apr 8. PMID: 33833384; PMCID: PMC8550946.

Brunetti L, Di Battista V, Venanzi A, Schiavoni G, Martelli MP, Ascani S, Mecucci C, Tiacci E, Falini B. Blastic plasmacytoid dendritic cell neoplasm and chronic myelomonocytic leukemia: a shared clonal origin. Leukemia. 2017 May;31(5):1238-1240. doi: 10.1038/leu.2017.38. Epub 2017 Jan 23. PMID: 28111467.

Patnaik MM, Lasho T, Howard M, Finke C, Ketterling RL, Al-Kali A, et al. Biallelic inactivation of the retinoblastoma gene results in transformation of chronic myelomonocytic leukemia to a blastic plasmacytoid dendritic cell neoplasm: shared clonal origins of two aggressive neoplasms. Blood Cancer J. 2018;8:82.

Khoury JD, Takeuchi K, Gru A, Ottou FG. Blastic plasmacytoid dendritic cell neoplasm. In: WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. Lyon (France): International Agency for Research on Cancer; 2024. (WHO classification of tumours series, 5th ed.; vol. 11). https://publications.iarc.who.int/637.

Vitte, Franck, et al. "Specific skin lesions in chronic myelomonocytic leukemia: a spectrum of myelomonocytic and dendritic cell proliferations. A study of 42 cases." The American journal of surgical pathology 36.9 (2012): 1302-1316.

Wang, Wei, et al. "Immunophenotypic and molecular features of acute myeloid leukemia with plasmacytoid dendritic cell differentiation are distinct from blastic plasmacytoid dendritic cell neoplasm." *Cancers* 14.14 (2022): 3375.

Griffin GK, Booth CAG, Togami K, Chung SS, Ssozi D, Verga JA, Bouyssou JM, Lee YS, Shanmugam V, Hornick JL, LeBoeuf NR, Morgan EA, Bernstein BE, Hovestadt V, van Galen P, Lane AA. Ultraviolet radiation shapes dendritic cell leukaemia transformation in the skin. Nature. 2023 Jun;618(7966):834-841. doi: 10.1038/s41586-023-06156-8. Epub 2023 Jun 7. PMID: 37286599; PMCID: PMC10284703.

CMML Criteria

WHO 5th Edition	ICC 2022
Essential criteria	Monocytosis defined as monocytes ≥ 0.5×10^9/L and ≥ 10% of the WBC
1. Persistent absolute (≥ 0.5×10^9/L) and relative (≥ 10%) peripheral blood monocytosis 2. Blasts constitute < 20% of the cells in the peripheral blood and bone marrow 3. Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms 4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (e.g. PDGFRA, PDGFRB, FGFR1, or JAK2)	Cytopenia (thresholds same as MDS)
Desirable criteria	Blasts (including promonocytes) < 20% of the cells in blood and bone marrow
1. Dysplasia involving ≥ 1 myeloid lineages 2. Acquired clonal cytogenetic or molecular abnormality 3. Abnormal partitioning of peripheral blood monocyte subsets	Presence of clonality: abnormal cytogenetics and/or presence of at least one myeloid neoplasm associated mutation of at least 10% allele frequency‡
Requirements for diagnosis	In cases without evidence of clonality, monocytes ≥ 1.0×10^9/L and > 10% of the WBC, and increased blasts (including promonocytes), or morphologic dysplasia, or an abnormal immunophenotype consistent with CMML would be required for its diagnosis.
· Essential criteria must be present in all cases · If monocytosis is ≥ 1×10^9/L: one or more desirable criteria must be met · If monocytosis is < 1×10^9/L: desirable criteria 1 and 2 must be met	Bone marrow examination with morphologic findings consistent with CMML (hypercellularity due to a myeloid proliferation often with increased monocytes), and lacking diagnostic features of acute myeloid leukemia, MPN or other conditions associated with monocytosis
Subtyping criteria	No BCR::ABL1 or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions
· Myelodysplastic CMML: WBC count < 13×10^9/L · Myeloproliferative CMML: WBC count ≥ 13×10^9/L	