EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

Department of
Pathology and
Laboratory
Medicine

GAP
Georgia Association of Pathology

2020 Virtual Pathology Course

08/22/2020

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Hematopathologist

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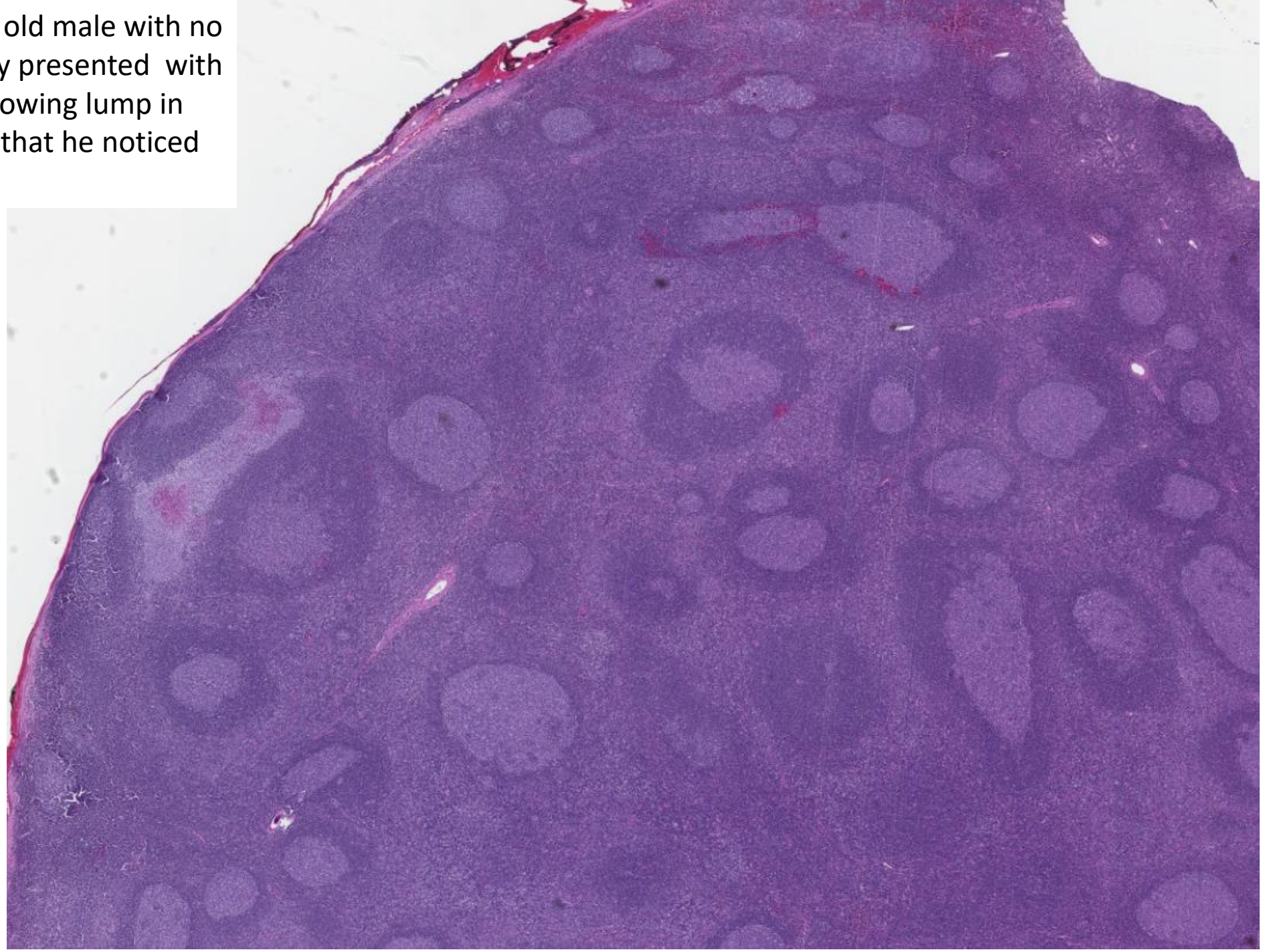
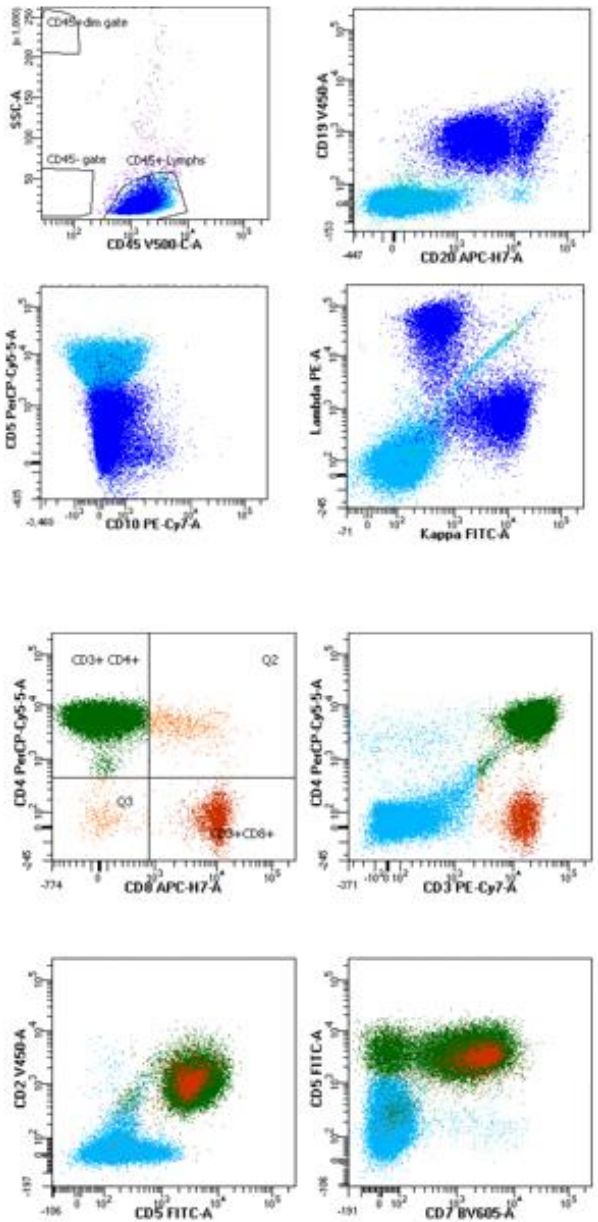
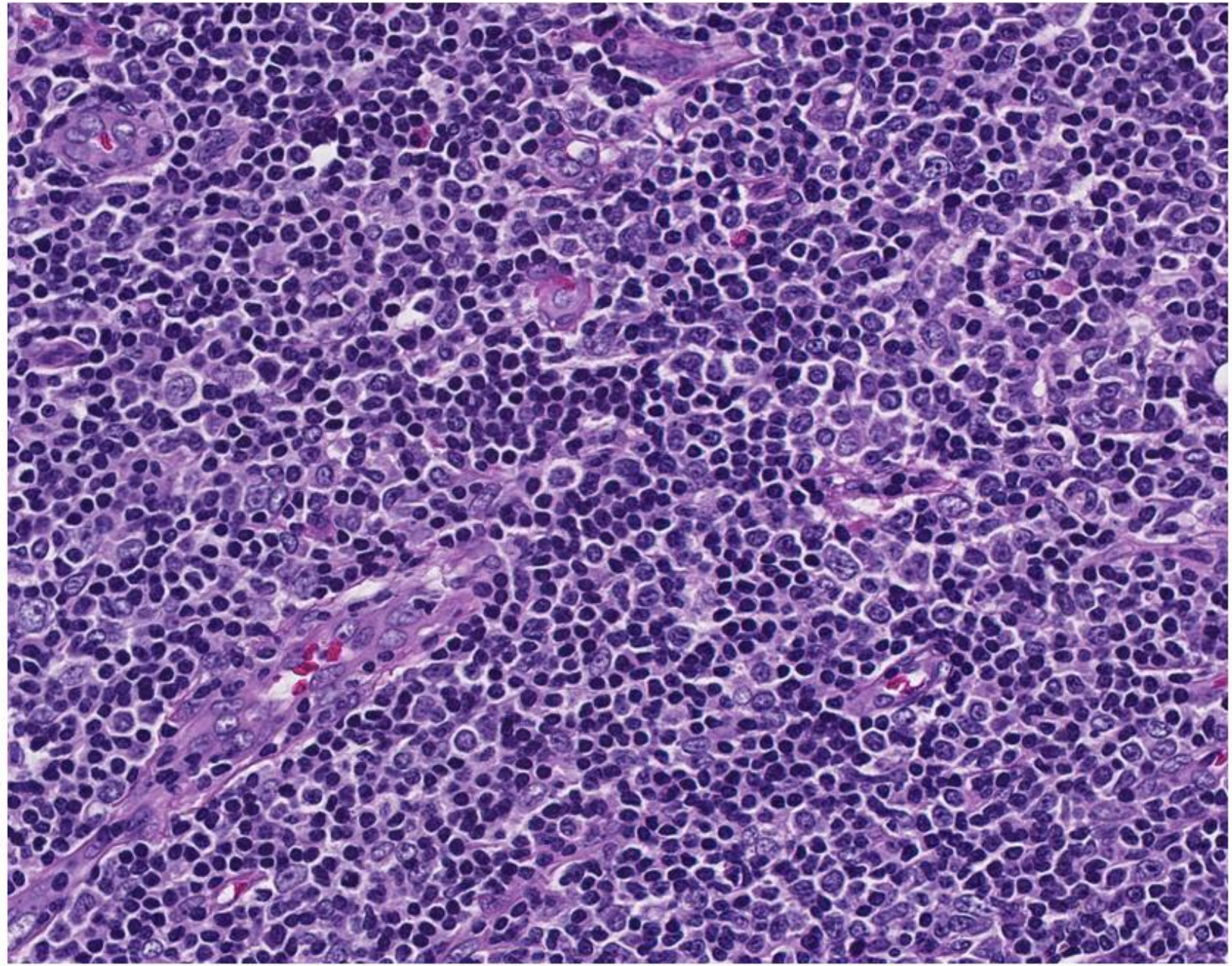
Disclosure

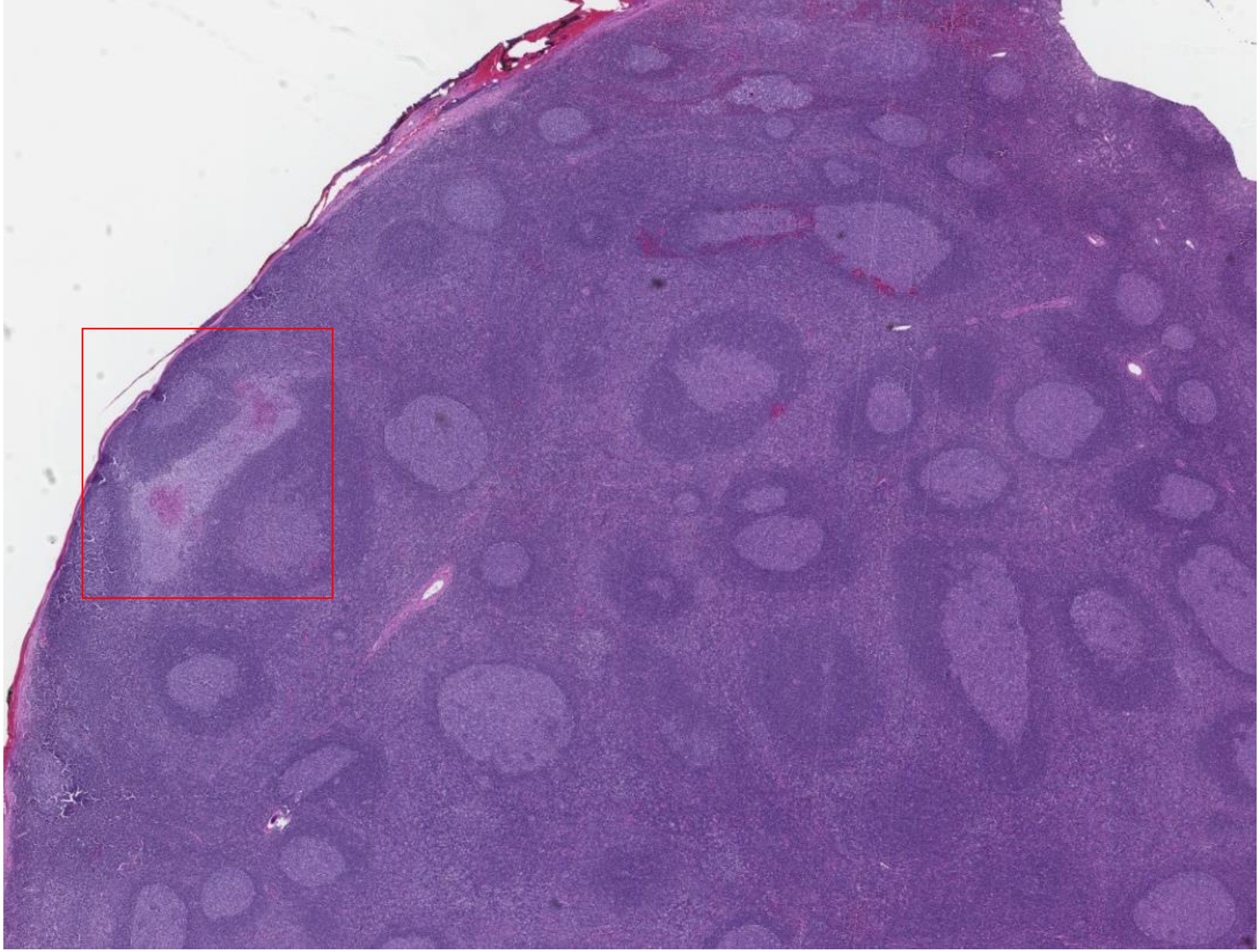
- No conflict of interest to disclose

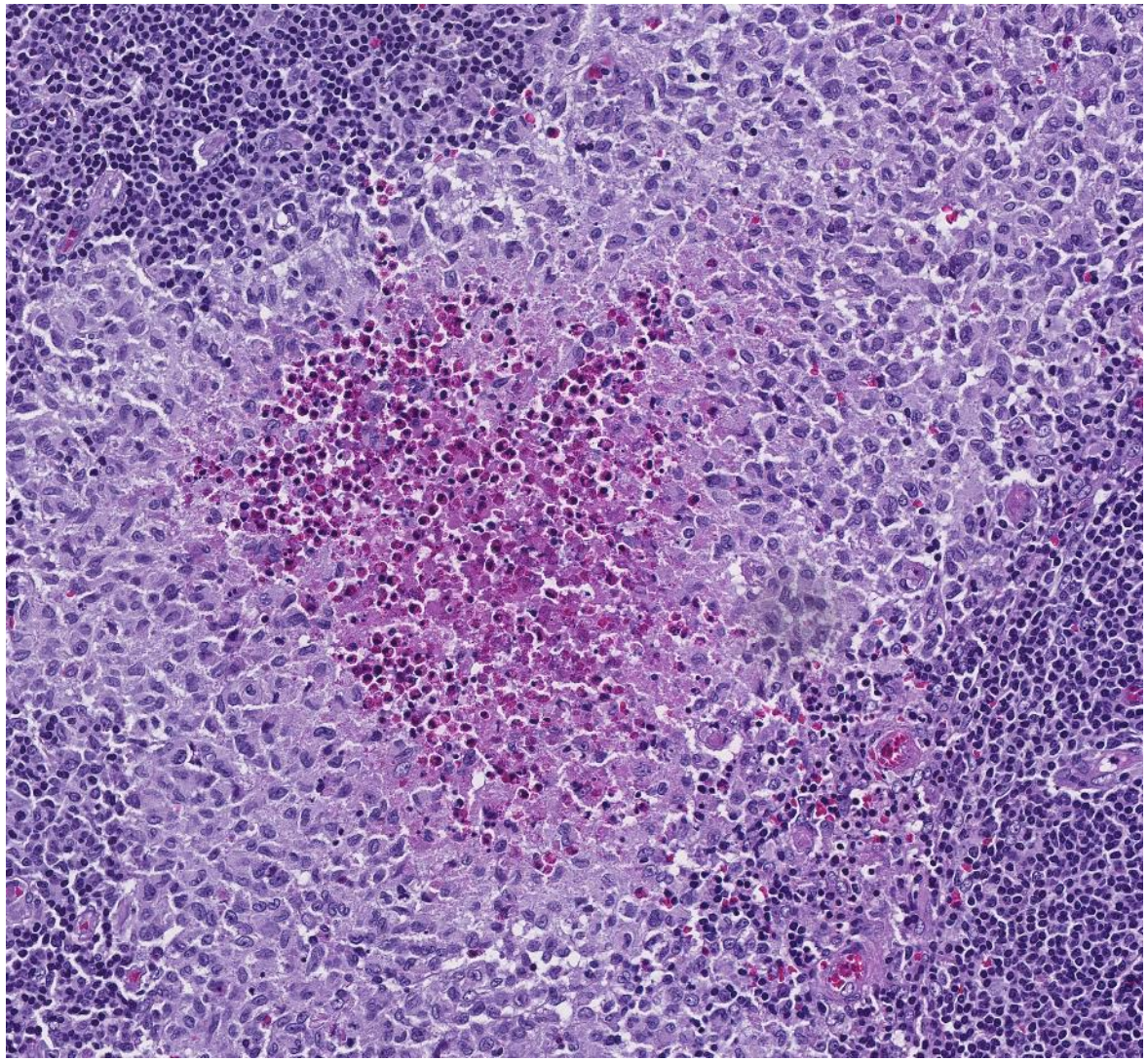
Case #13 A 44 year old male with no past medical history presented with a painless slowly growing lump in front of his left ear that he noticed one year prior.

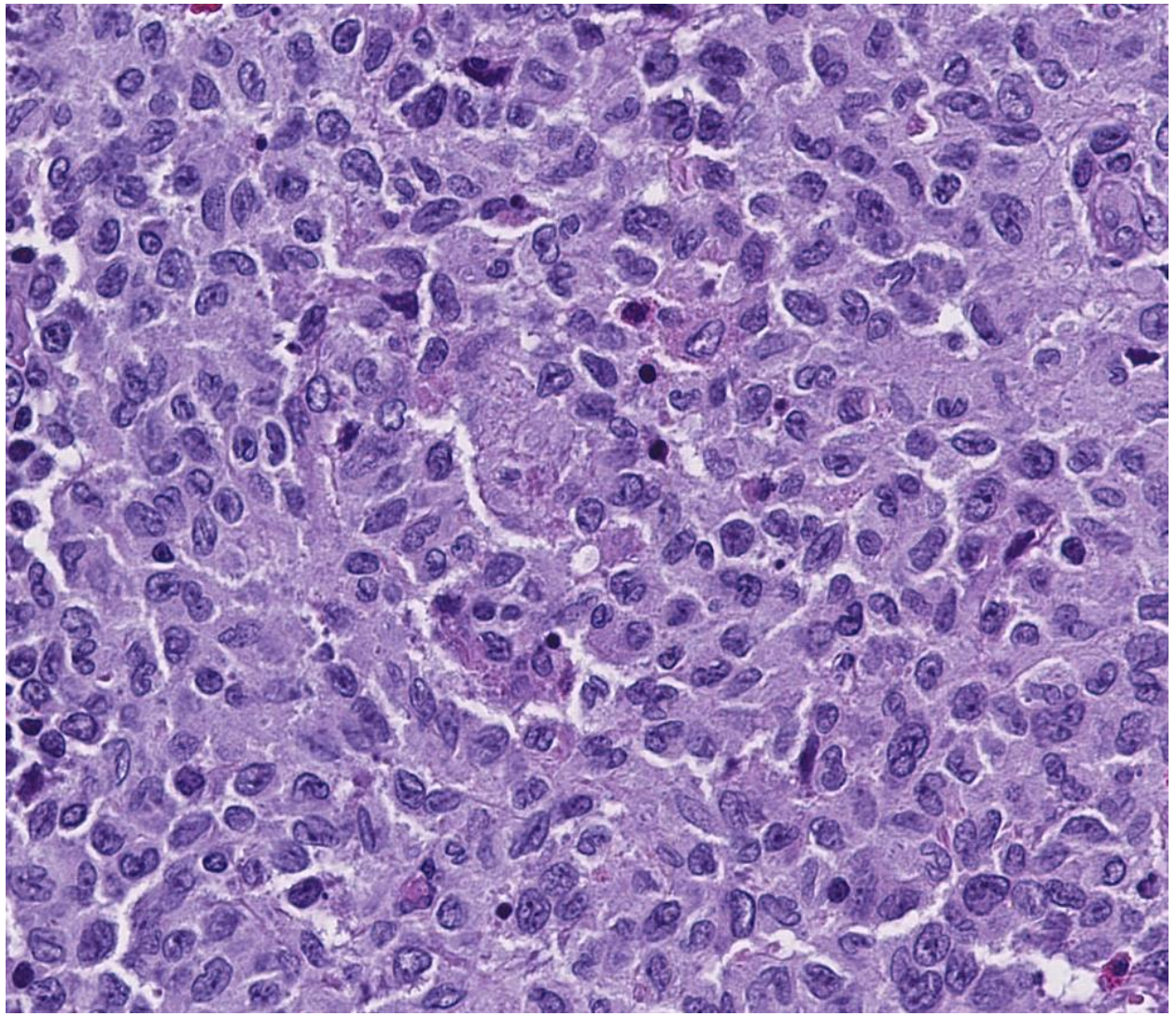



CD45+dim gate
SSC-A
CD45- gate
CD45+Lymphs
CD45 V500-C-A
CD19 V450-A
CD20 APC-H7-A
CD5 PerCP-Cy5-5-A
CD10 PE-Cy7-A
Lambda PE-A
Kappa FITC-A
CD3+ CD4+
Q2
Q3
CD3+CD8+
CD4 PerCP-Cy5-5-A
CD8 APC-H7-A
CD3 PE-Cy7-A
CD2 V450-A
CD5 FITC-A
CD5 FITC-A
CD7 BV605-A

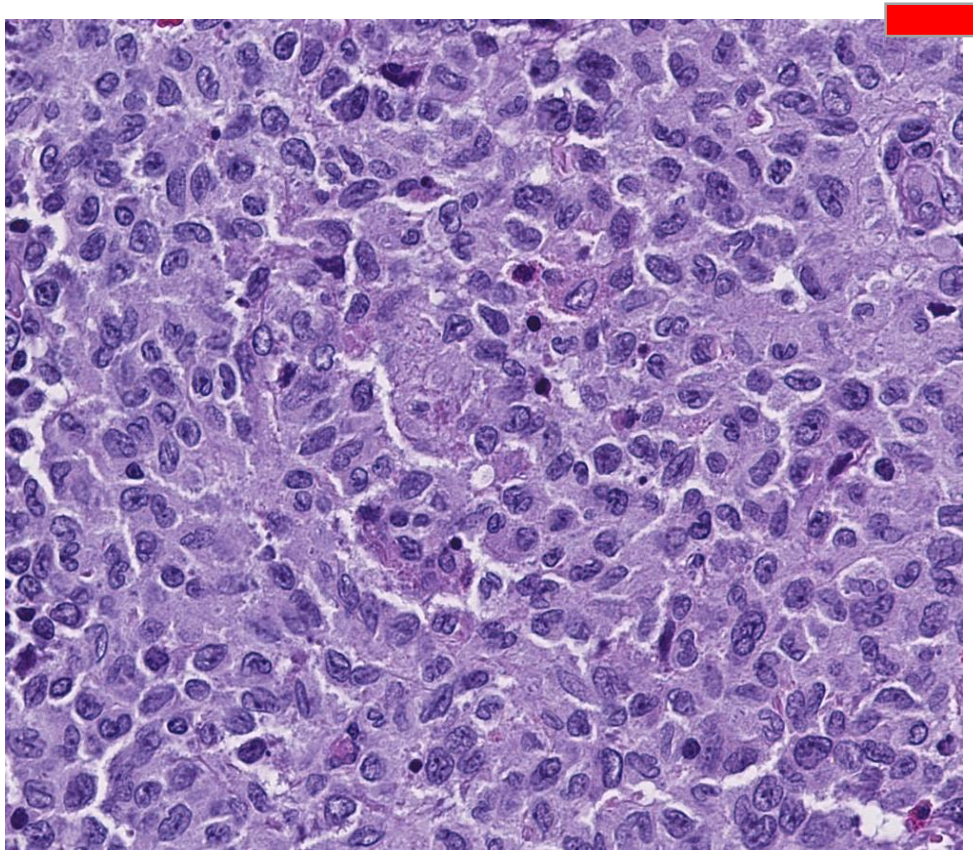








Histiocytes



- Cell of origin and classification
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Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

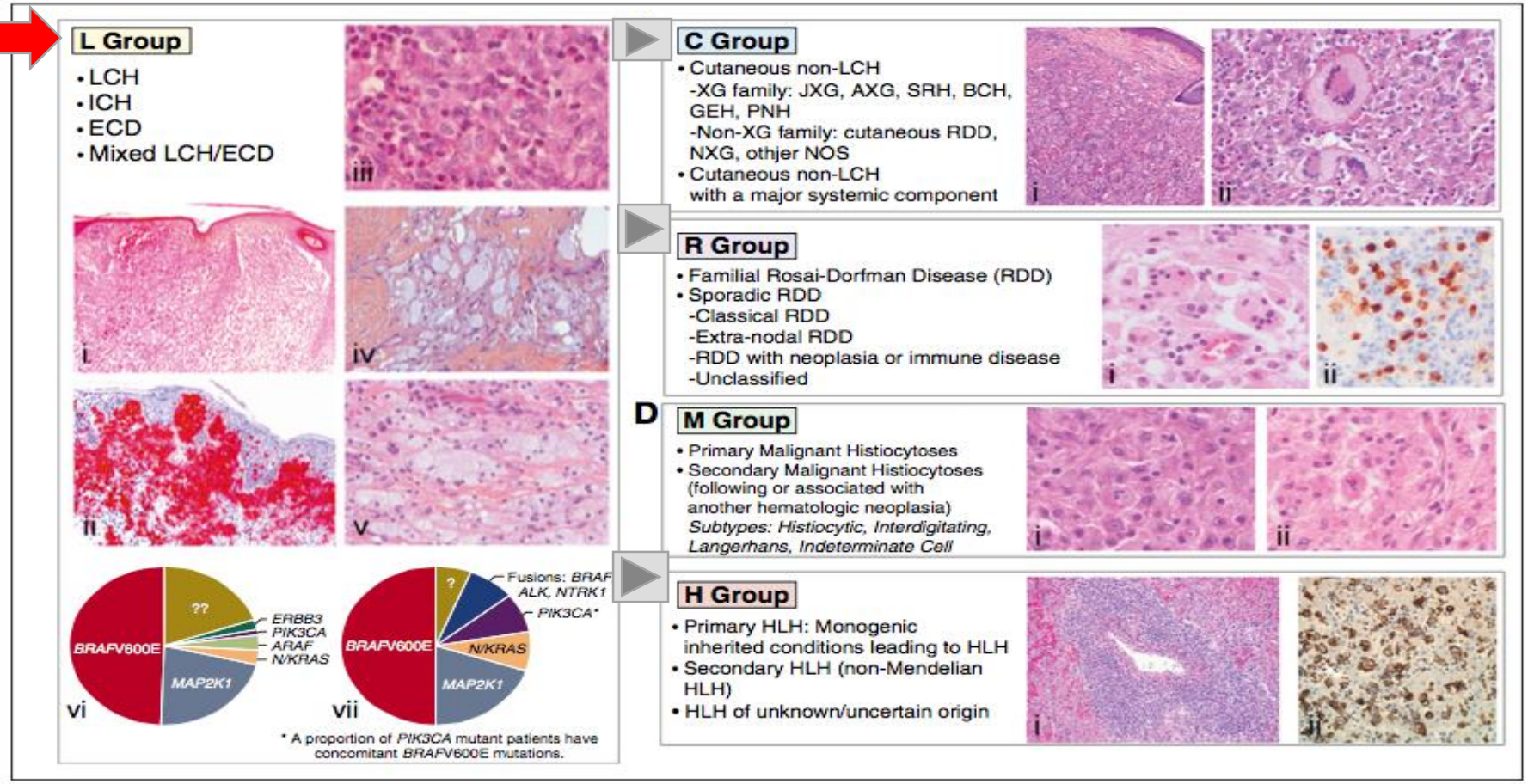
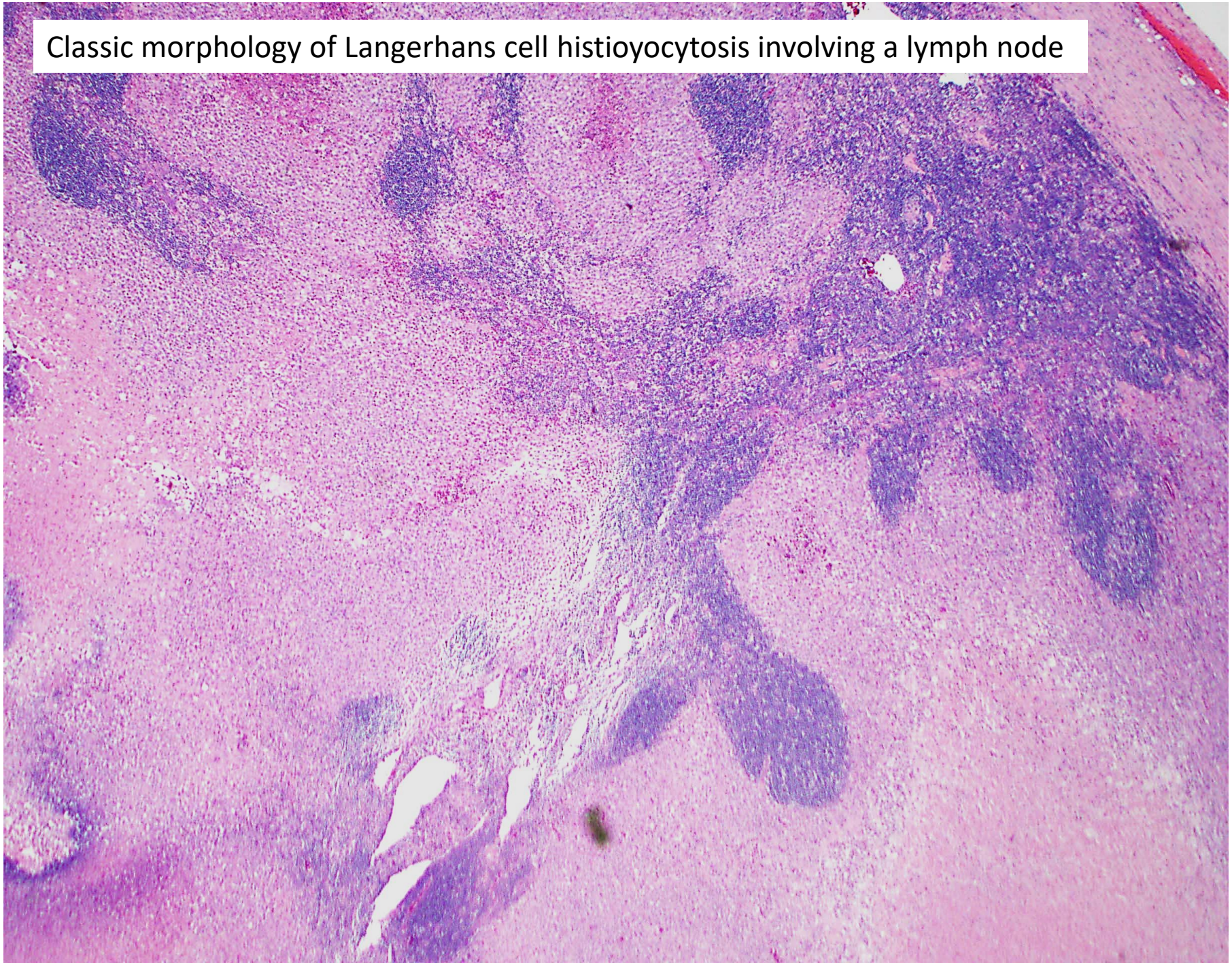
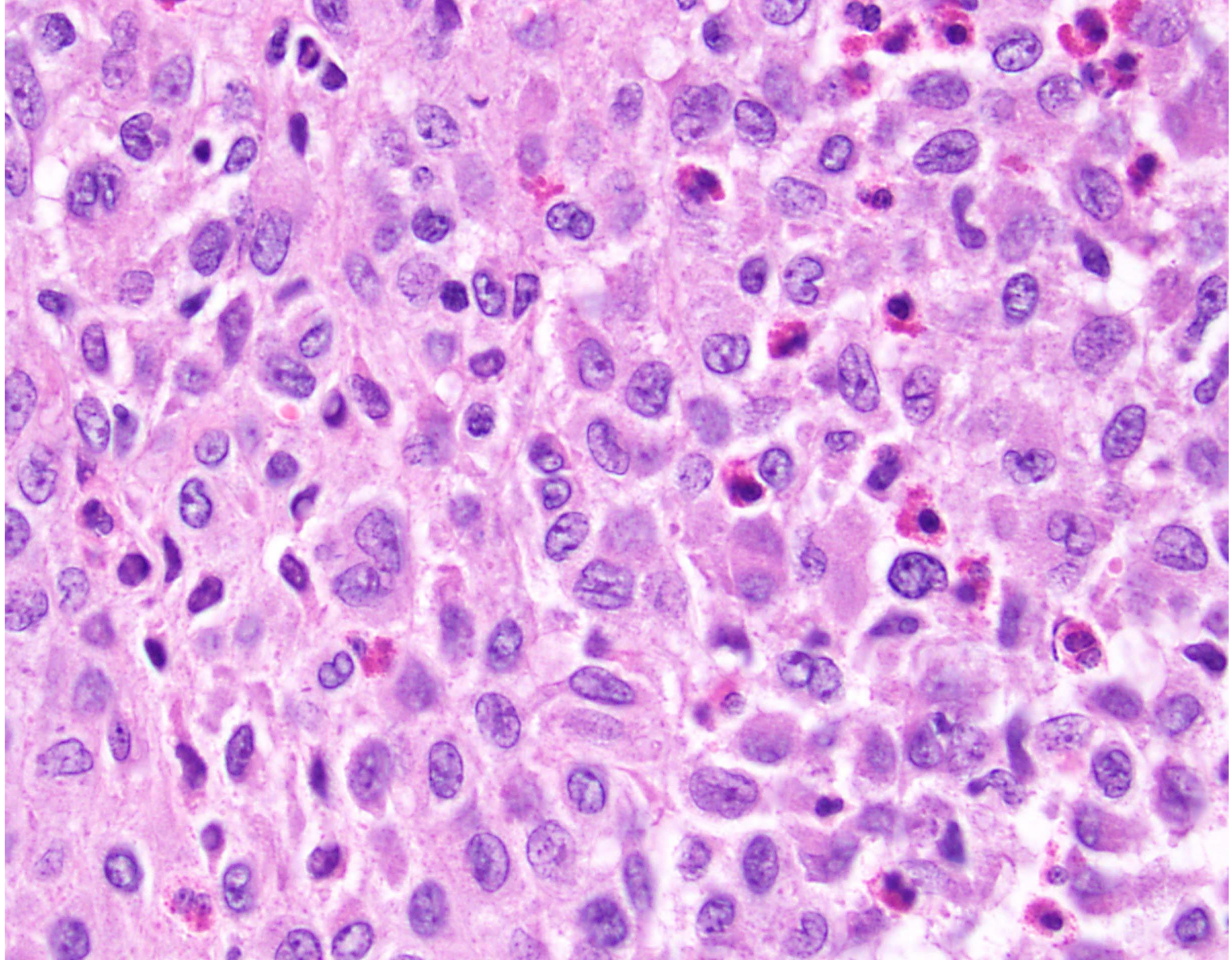


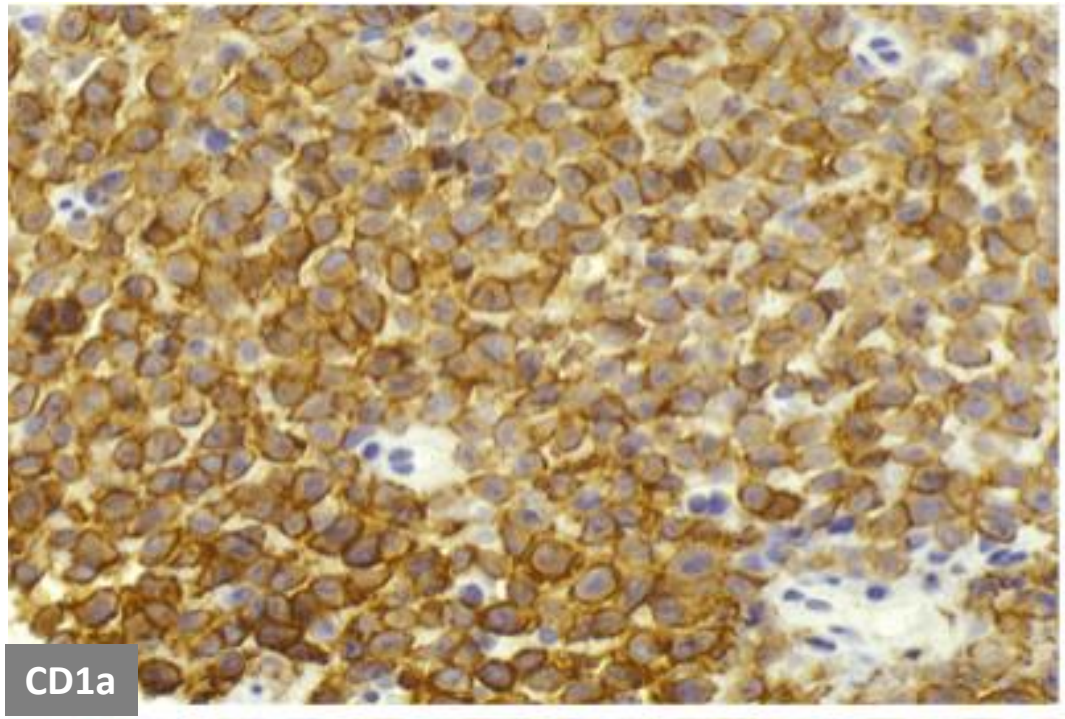
Figure 1. Histology and somatic mutations of histiocytoses of group L, C, R, M, and H. (A) L group: Histology of LCH (skin [i-ii] and bone [iii]) and of ECD (perirenal [iv-v]). Pie chart of relative frequencies of activating kinase mutations in LCH (vi) and ECD (vii). (B) C group: Histology of JXG (i-ii). (C) R group: Histology of RDD (meningeal with high IgG4$^+$ plasma cell infiltration [i-ii]). (D) M group: Histology of MH (i-ii). (E) H group: Histology of inherited HLH (liver [i-ii]). Staining with CD1a (Lii in red), IgG4 (Rii in brown), CD163 (Hii in brown), or hematoxylin and eosin (all others). NOS, not otherwise specified.

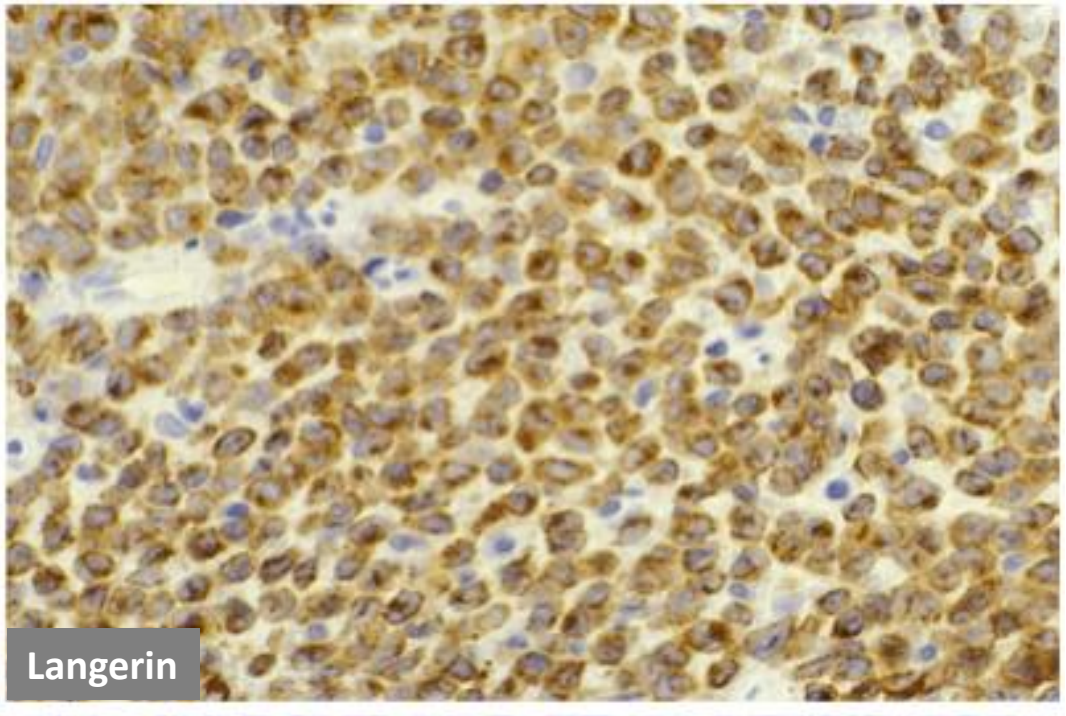
Cell type	origin	markers
Erdheim-Chester disease (Macrophages)	Bone marrow- myeloid progenitor	CD68, CD4, CD14, **CD163**, CD11c, S100 staining has been reported
Indeterminate cell histiocytosis	Unclear cell of origin	CD68, CD4, S100, MHC-II, CD1a
Langerhans cell histiocytosis (langerhans cells)	Yolk sac- embryonal liver Bone marrow derived-myeloid progenitor	CD68, CD4, MHC-II, S100, **CD1a**, **Langerin (CD207).**

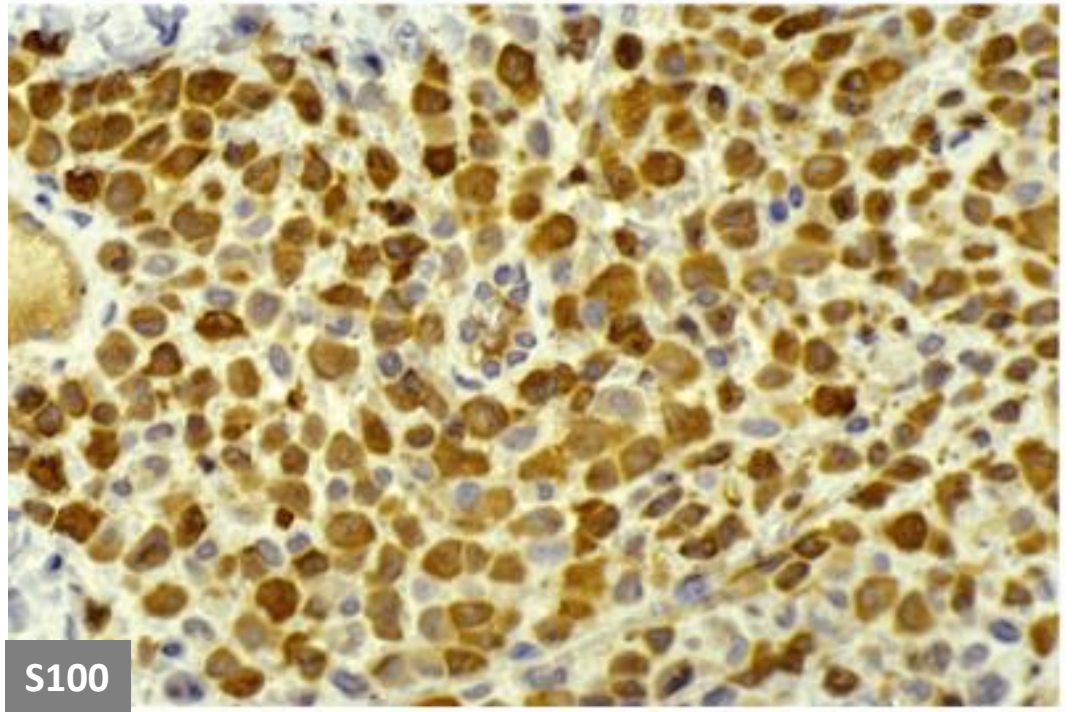
Classic morphology of Langerhans cell histioyocytosis involving a lymph node

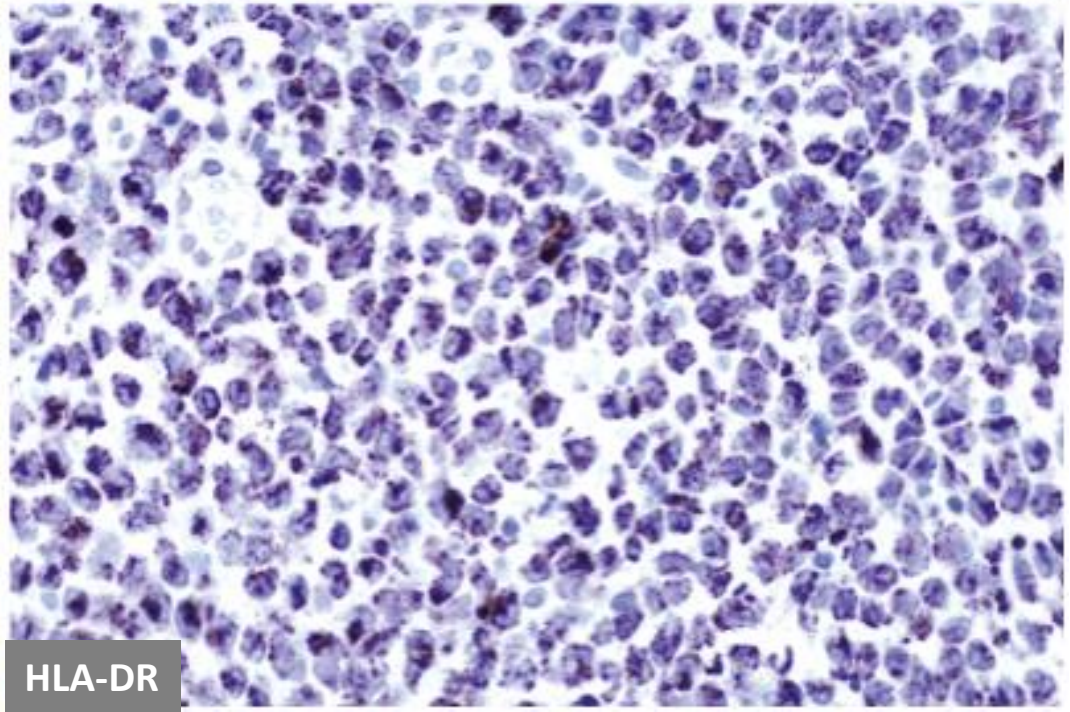


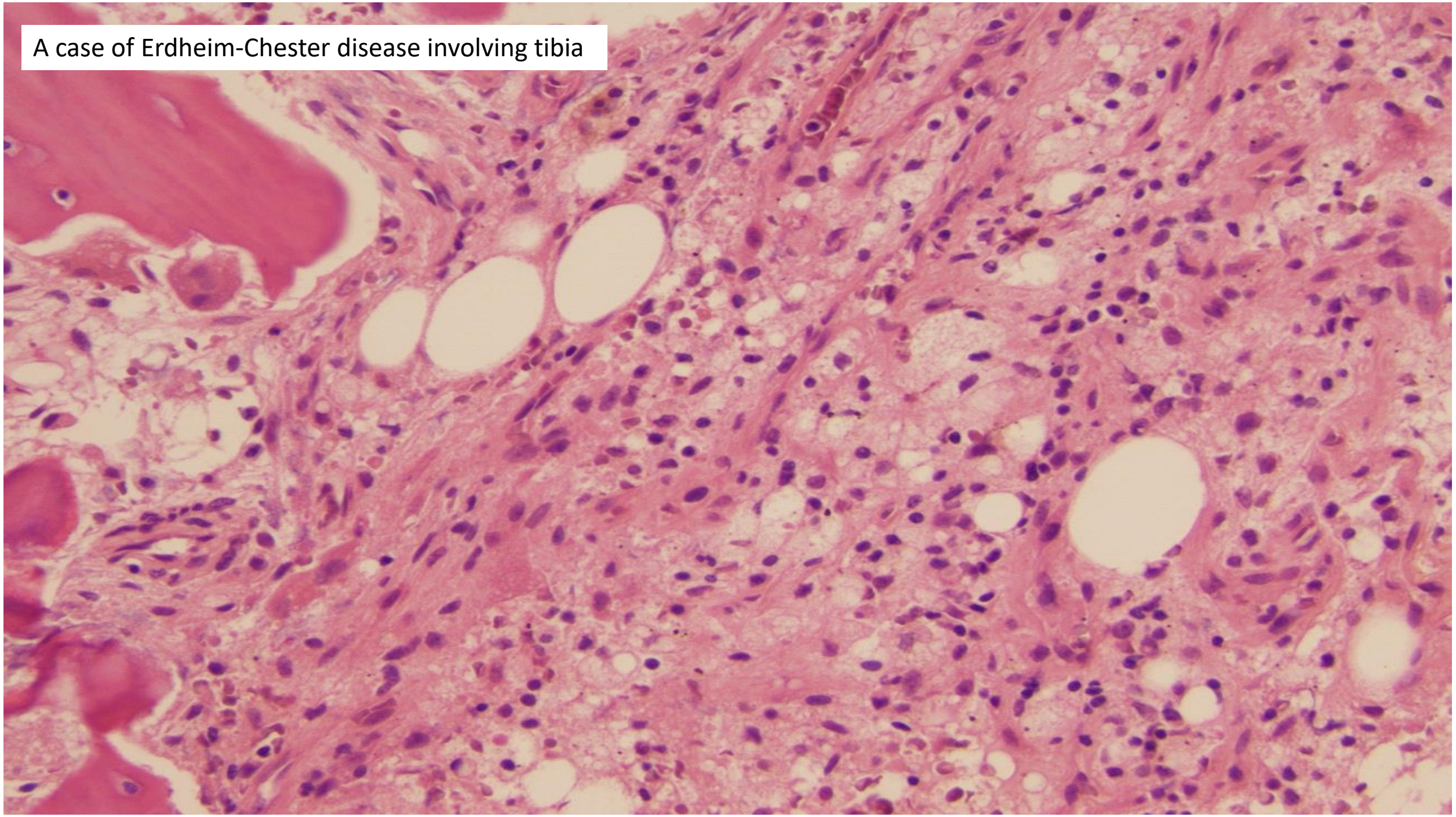


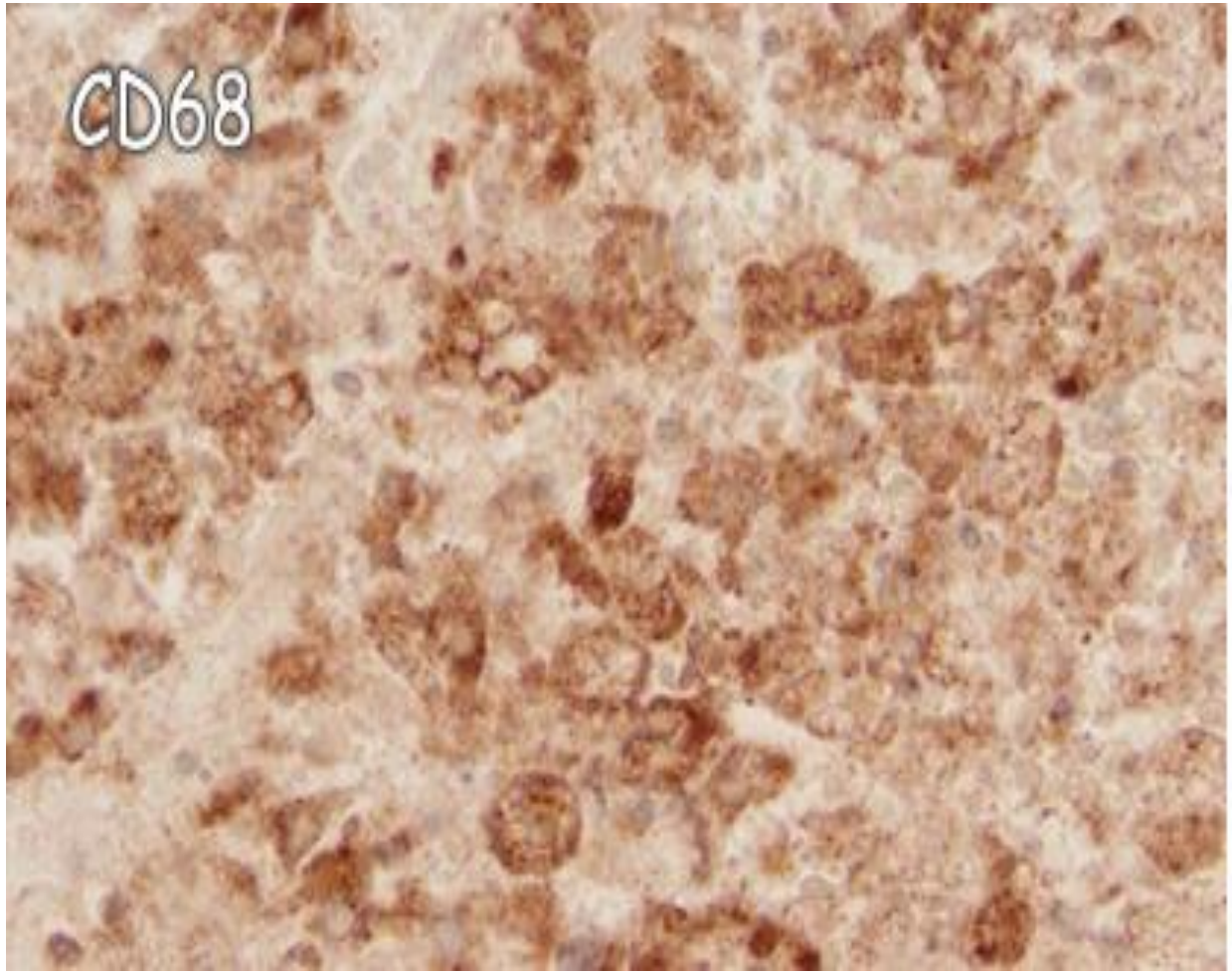

CD1a

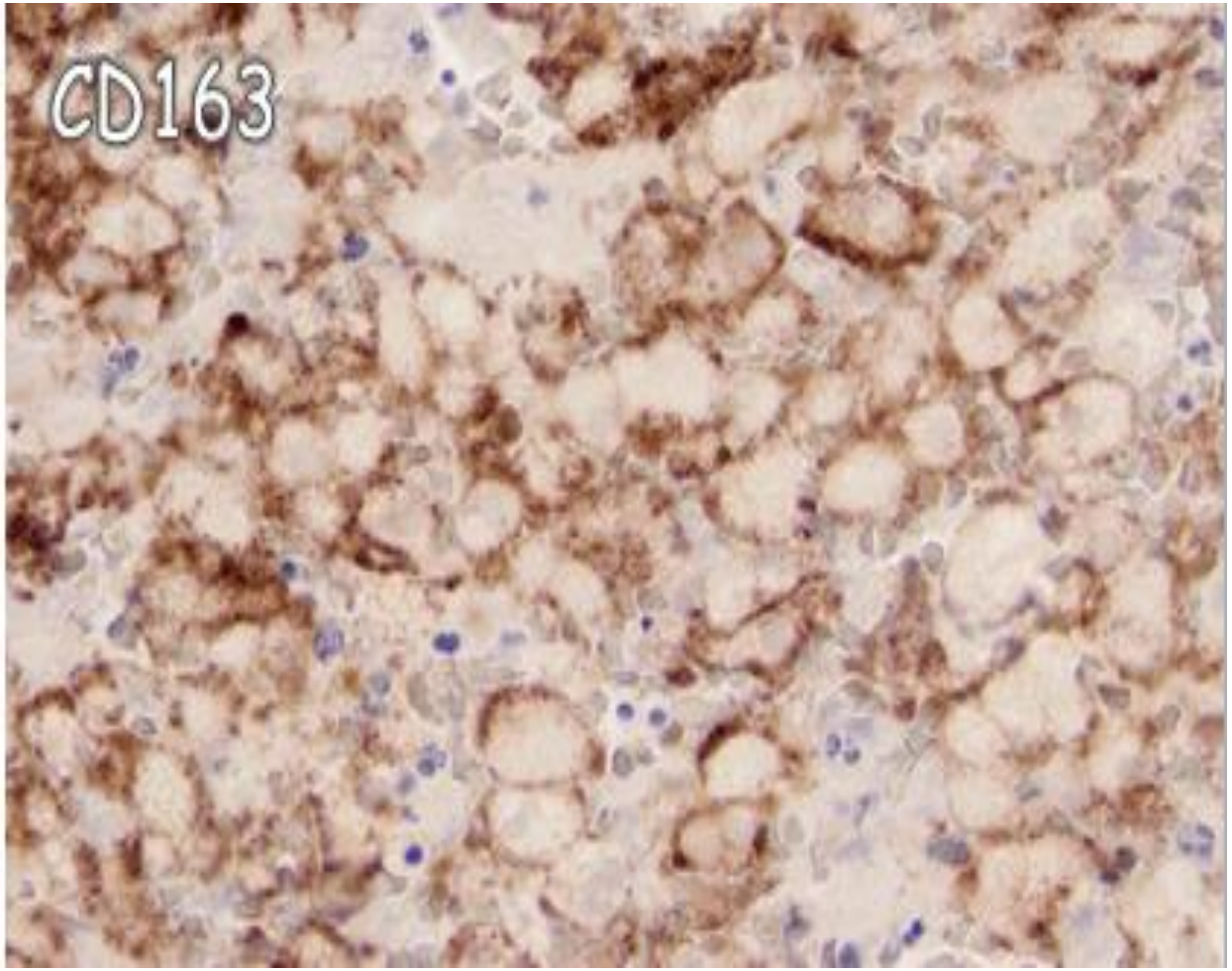

Langerin


S100

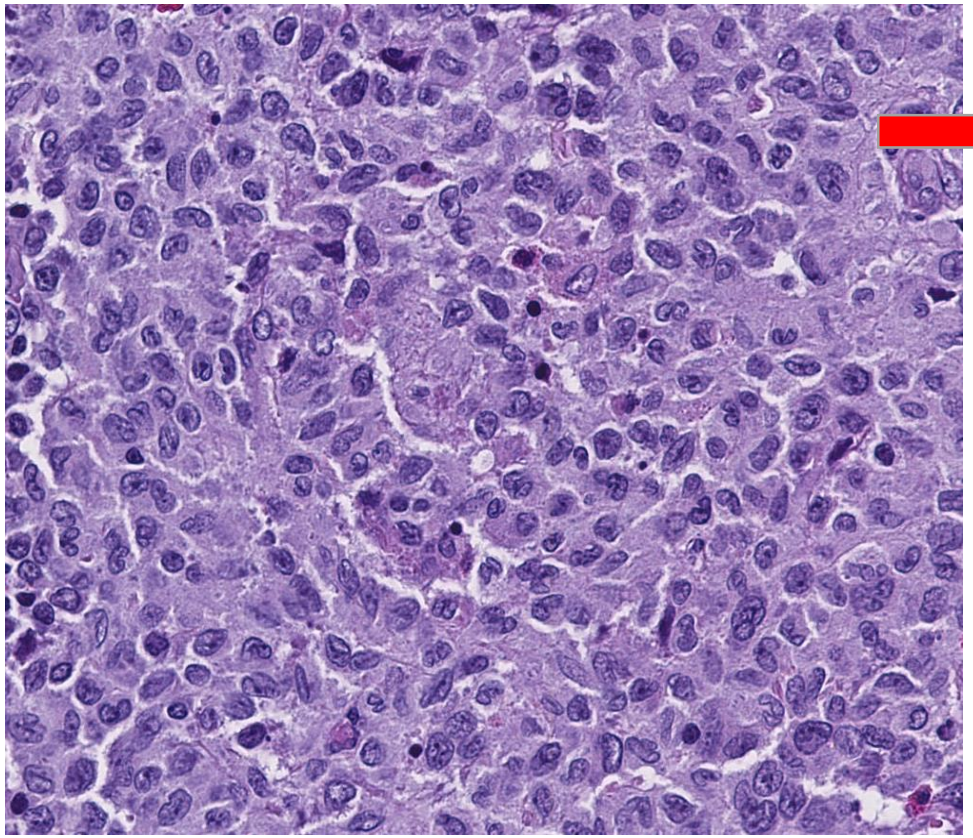

HLA-DR


A case of Erdheim-Chester disease involving tibia


CD68


CD163

Histiocytes



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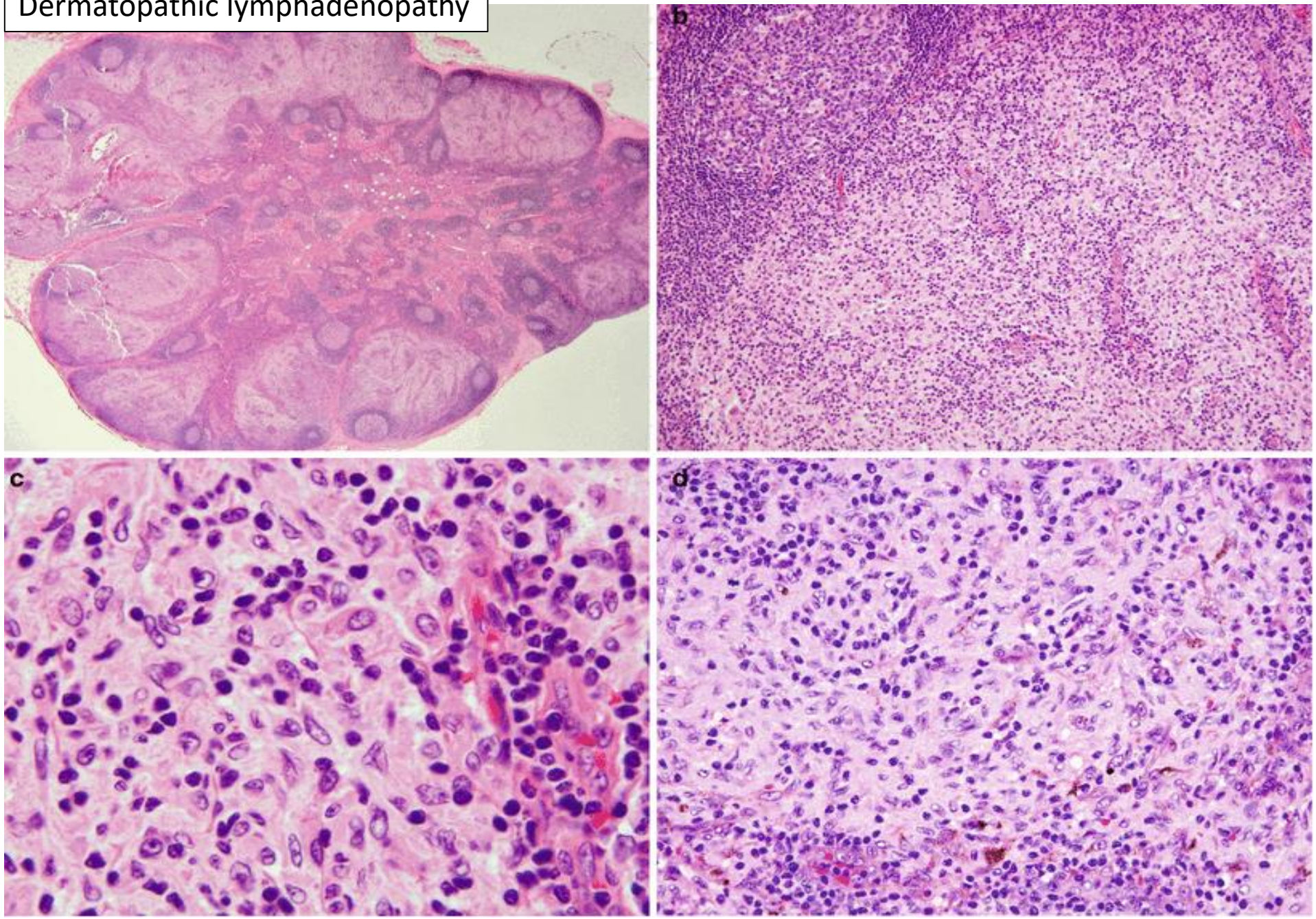
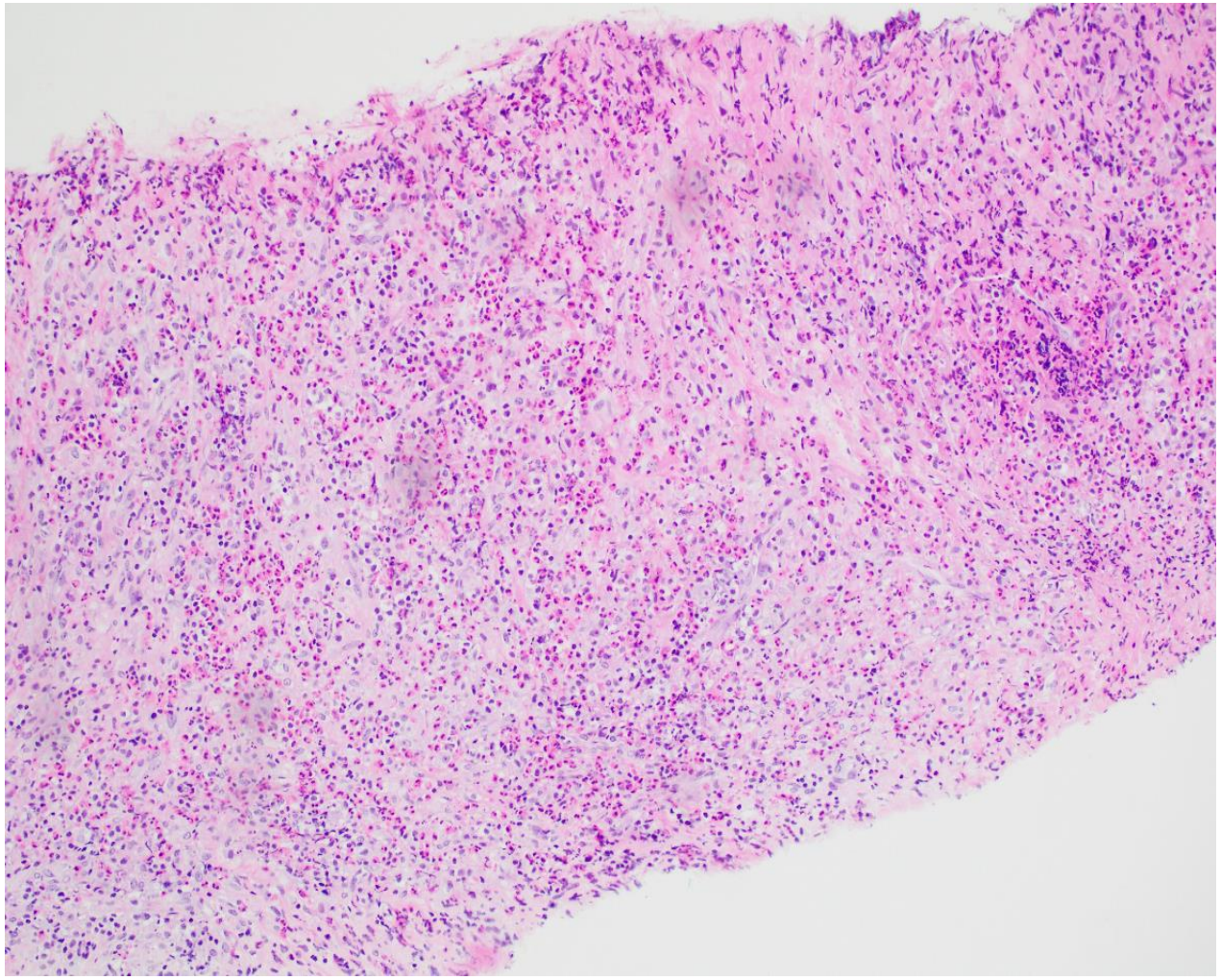
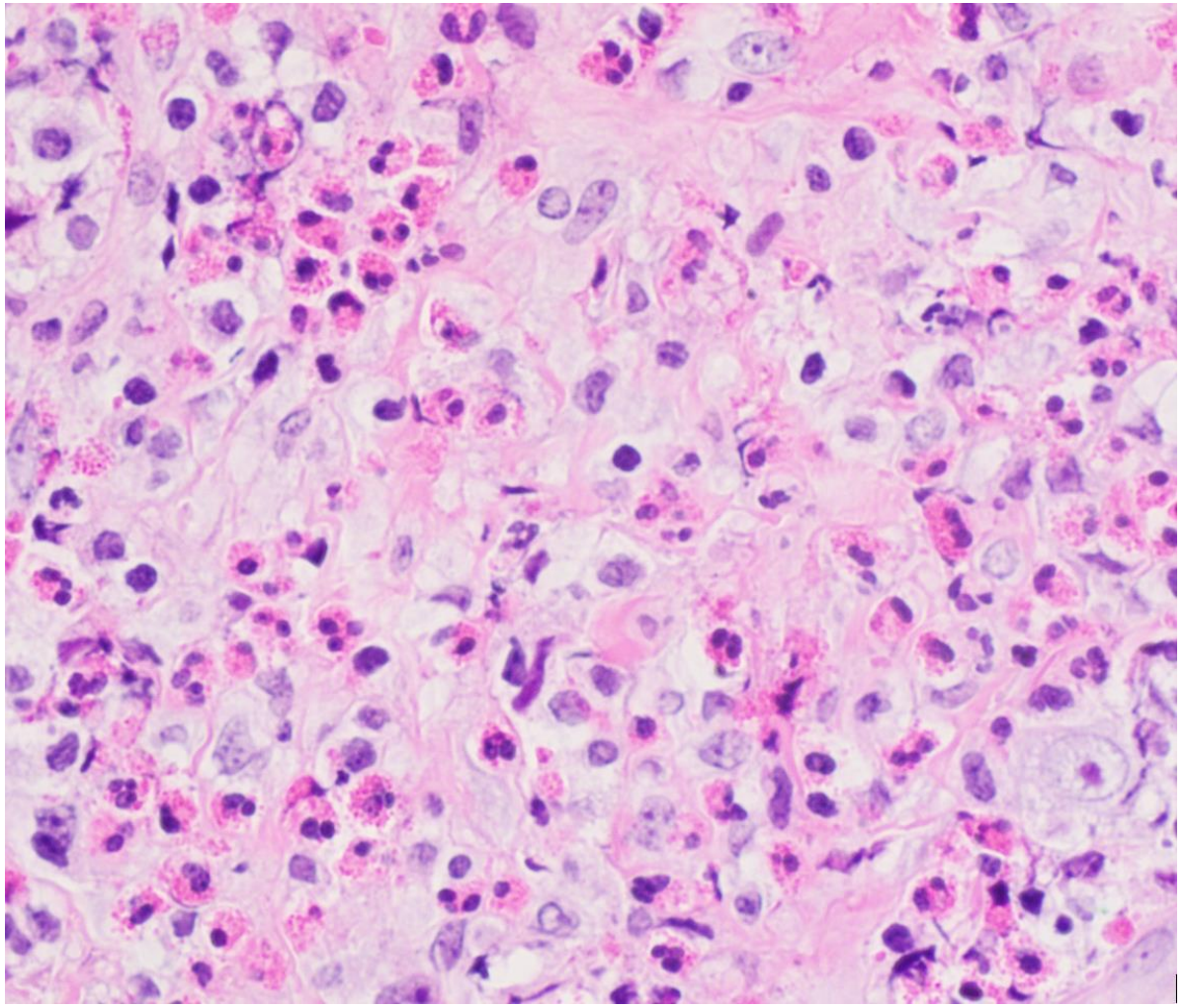
Dermatopathic lymphadenopathy

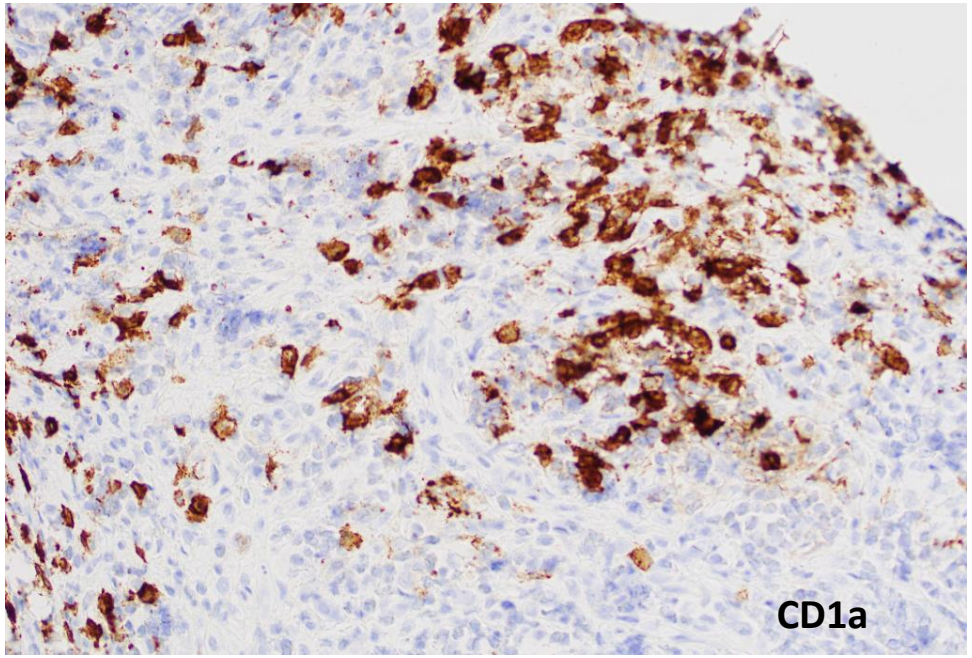


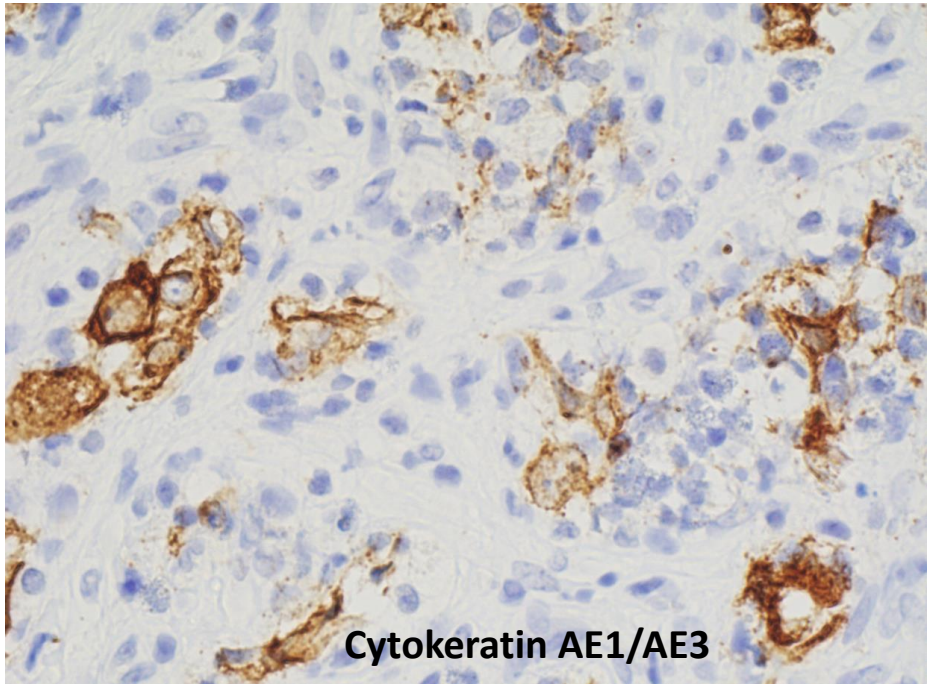
In: Atlas of Lymph Node Pathology. Atlas of Anatomic Pathology. Springer, New York, NY. https://doi.org/10.1007/978-1-4614-7959-8_31

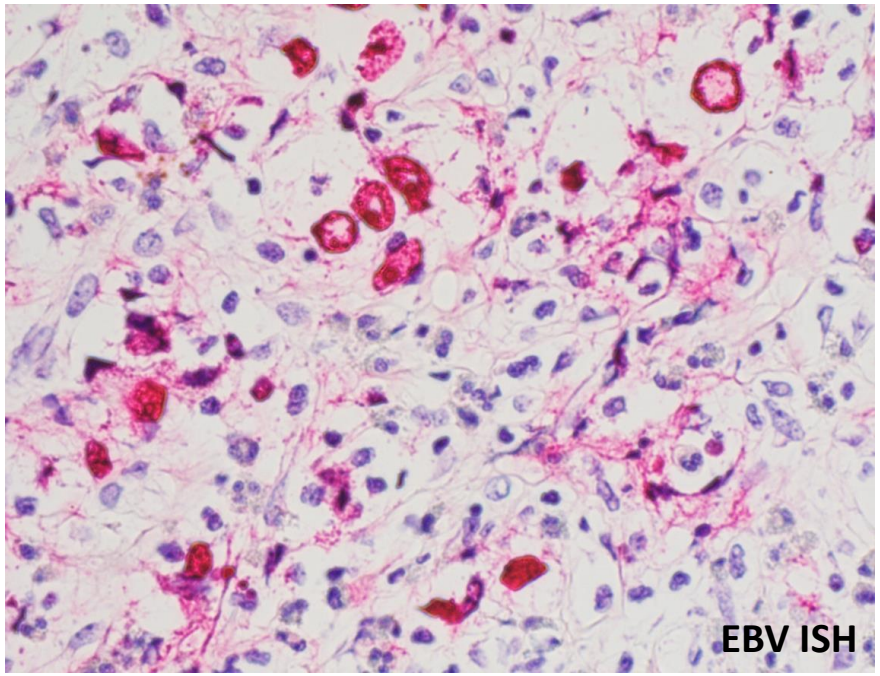
Reactive histiocytosis in a left neck mass core biopsy





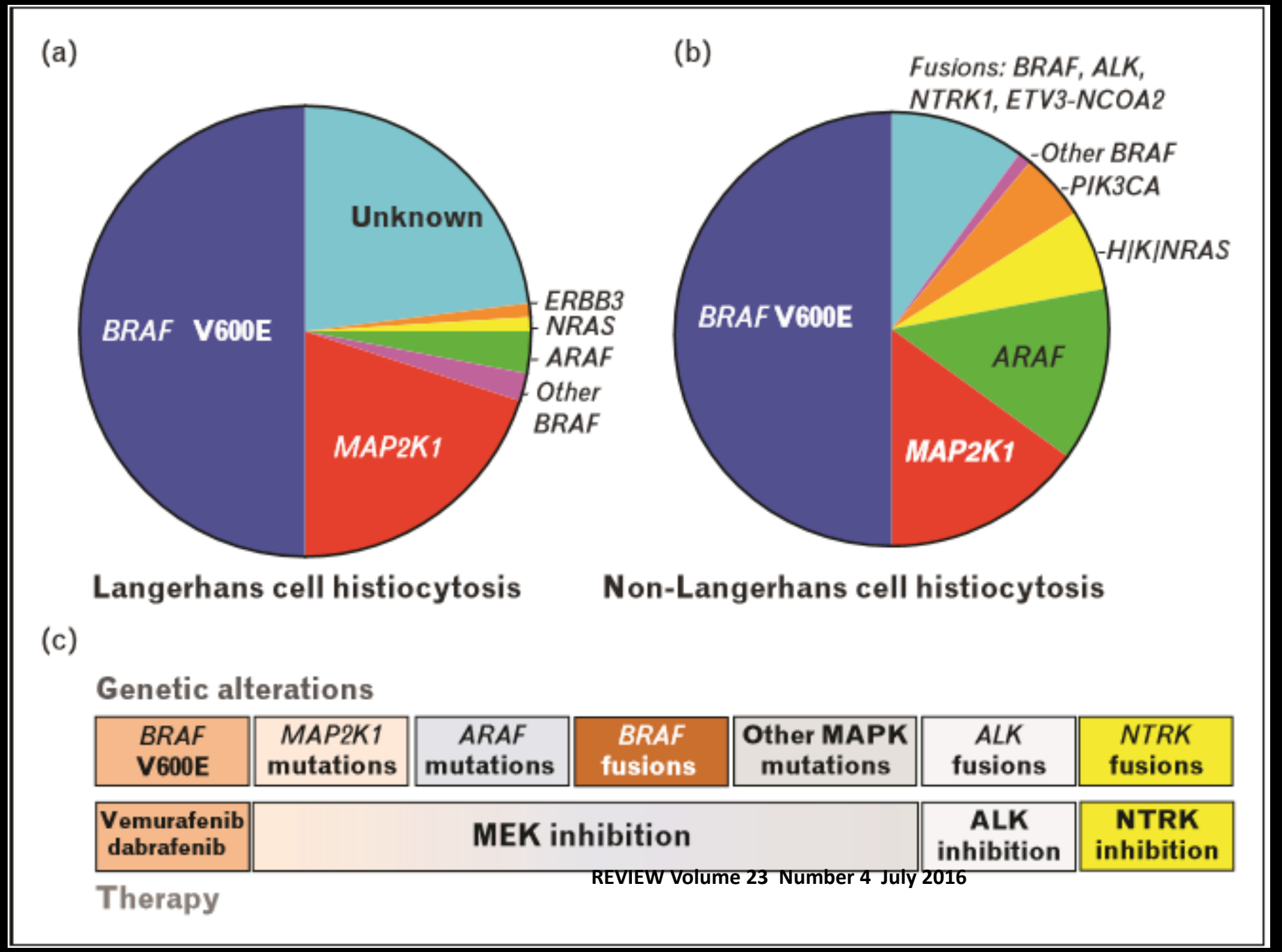






Dx Nasopharyngeal carcinoma

In challenging cases mutational analysis may be helpful in supporting a clonal process



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MAPK pathway mutations

- **B-Raf proto-oncogen:**

  In contrast to recurrent BRAF V600E mutations, other mutations in BRAF have been found only rarely in histiocytoses. These include BRAF V600D and BRAF V600insDLAT in LCH, BRAF F595L in histiocytic sarcoma

- **A-Raf Proto-oncogen:**

  Recurrent in non-LCH and are present in 21% of ECD.

- **RAS isoforms:**

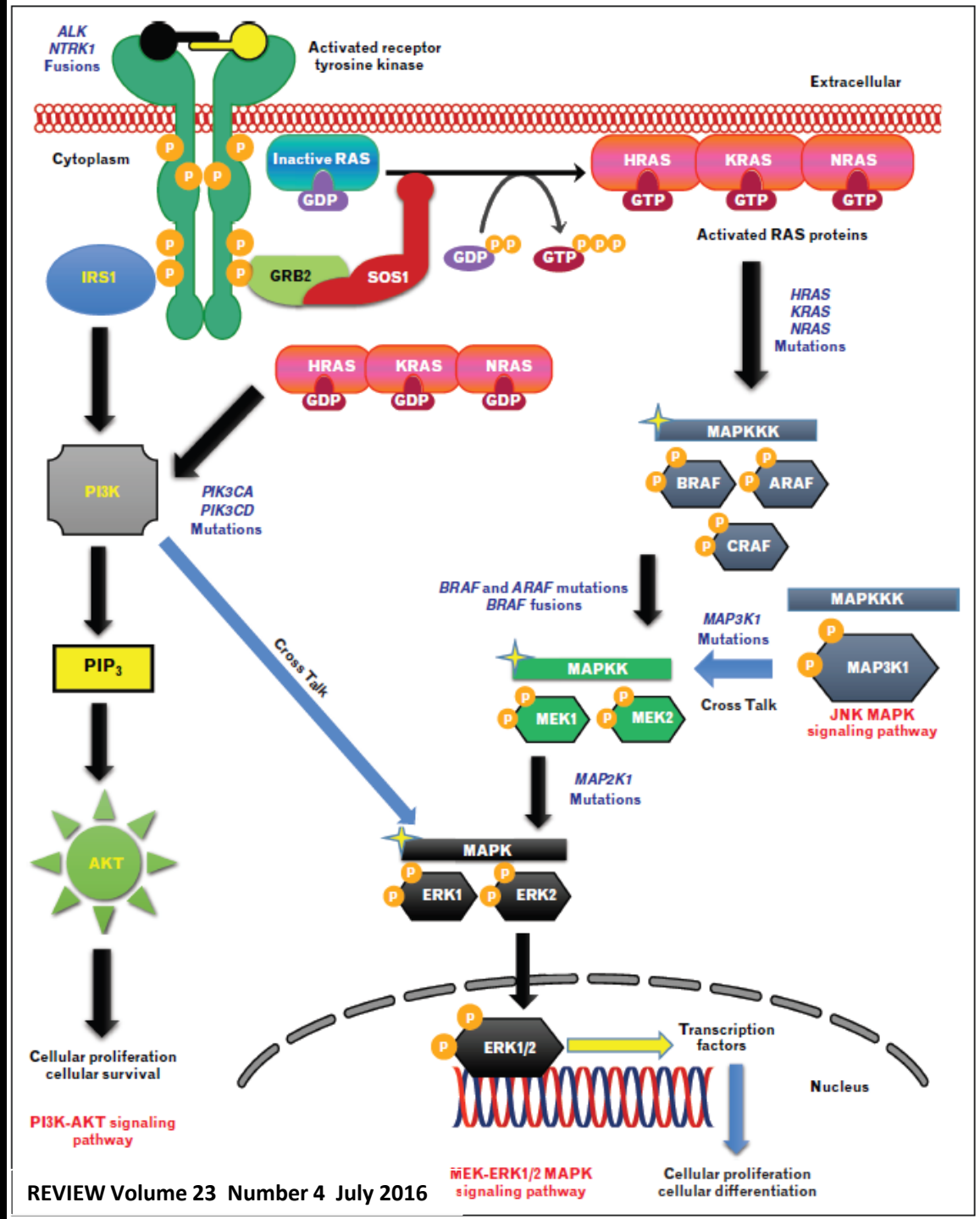
  This includes NRAS mutations in 3–7% of ECD and less frequently in LCH.

- **MAP2K1:**

  Recurrent in LCH and are present in 10–40% of LCH patients. MAP2K1 mutations are also present in non-LCH and occur in 14% of ECD.

- **PI3K mutation:**

  Activating PIK3CA mutations have been described in 17% of BRAF V600E-wildtype ECD



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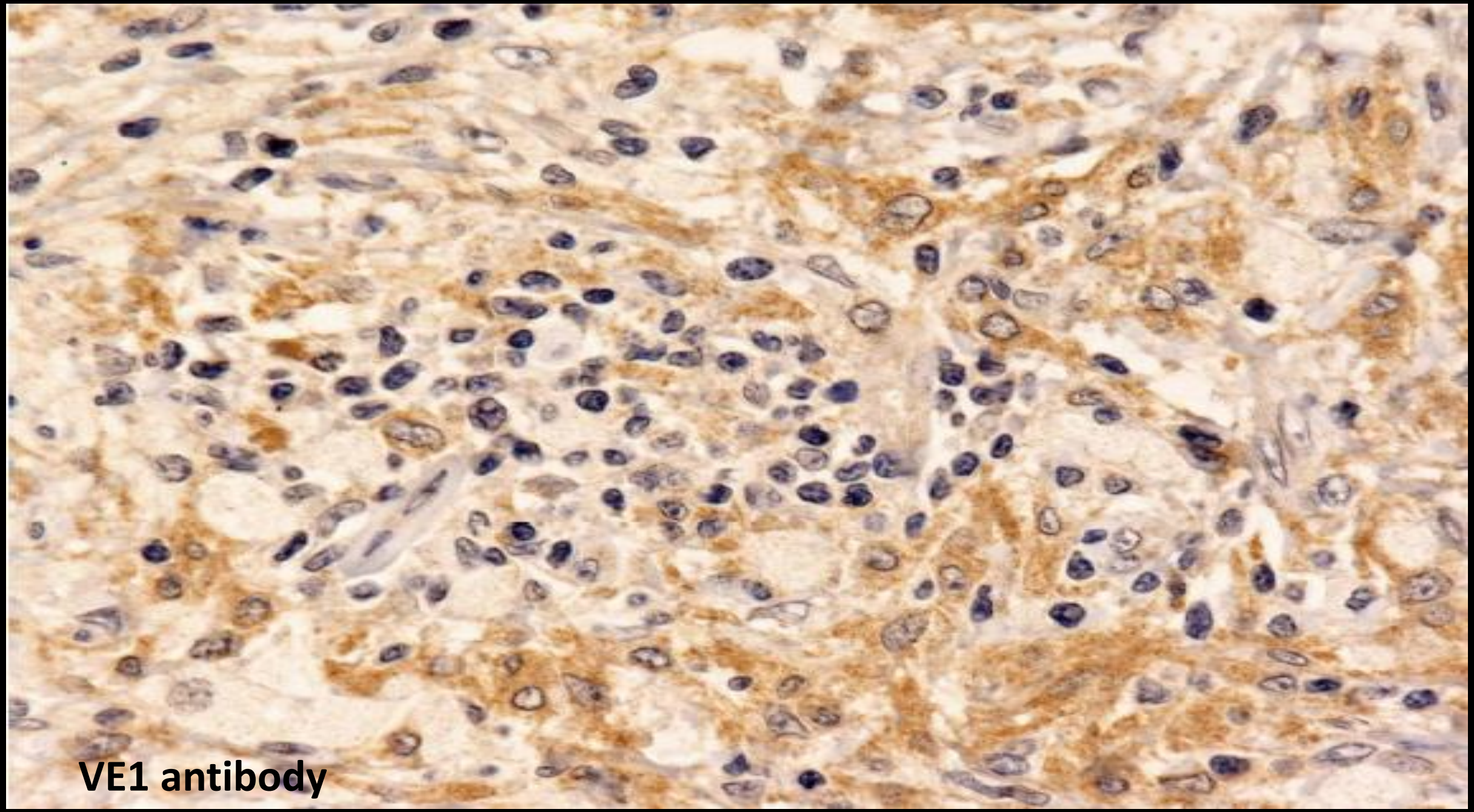

VE1 antibody

	THxID-BRAF kit	*cobas 4800 BRAF V600 mutation test*	*Sanger*	*HRM*	*Pyrosequencing*	*IHC*
CDx or LDT	CDx	CDx	LDT	LDT	LDT	LDT
Sensitivity, %	>96 for V600E; >92 for V600K	~97 for V600E; 66–70 for V600K	92–98	98–100	>98	85–100
Specificity, %	100	>98	100	98–100	90–100	98–100
Limit of detection, %	5 for V600E, V600K	5–7 for V600E; >35 for V600K	6.6	6.6	5	5
Mutations detected	Approved for V600E, V600K	Approved for V600E only	99% of all detectable mutations	99% of all detectable mutations	Assay optimized for V600 mutations is available	VE1 antibody specific for V600E
Sample	Tumor-derived DNA	Tumor-derived DNA	Tumor-derived DNA	Tumor-derived DNA	Tumor-derived DNA	Tissue
Cost	Medium	Medium	Medium	Low	High	Low

Cyclin-D1 staining in LCH

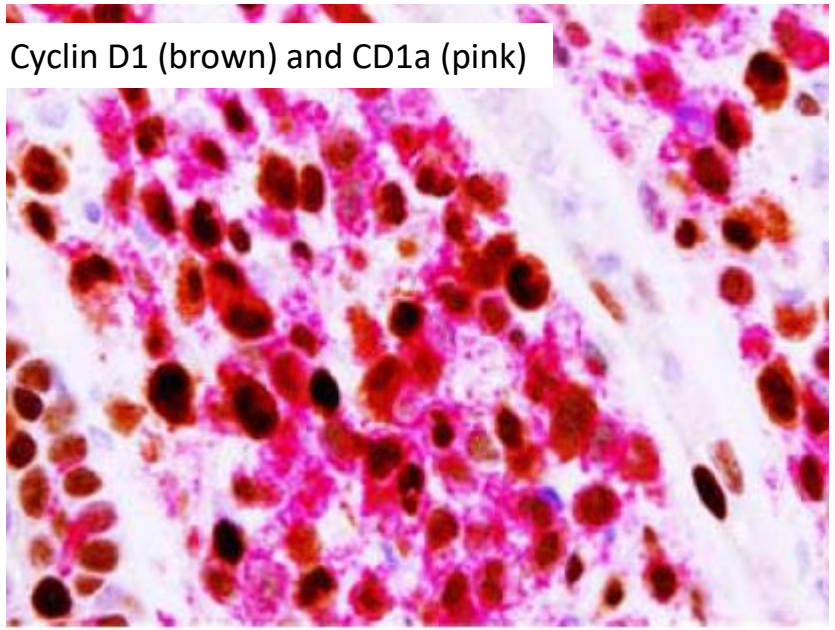
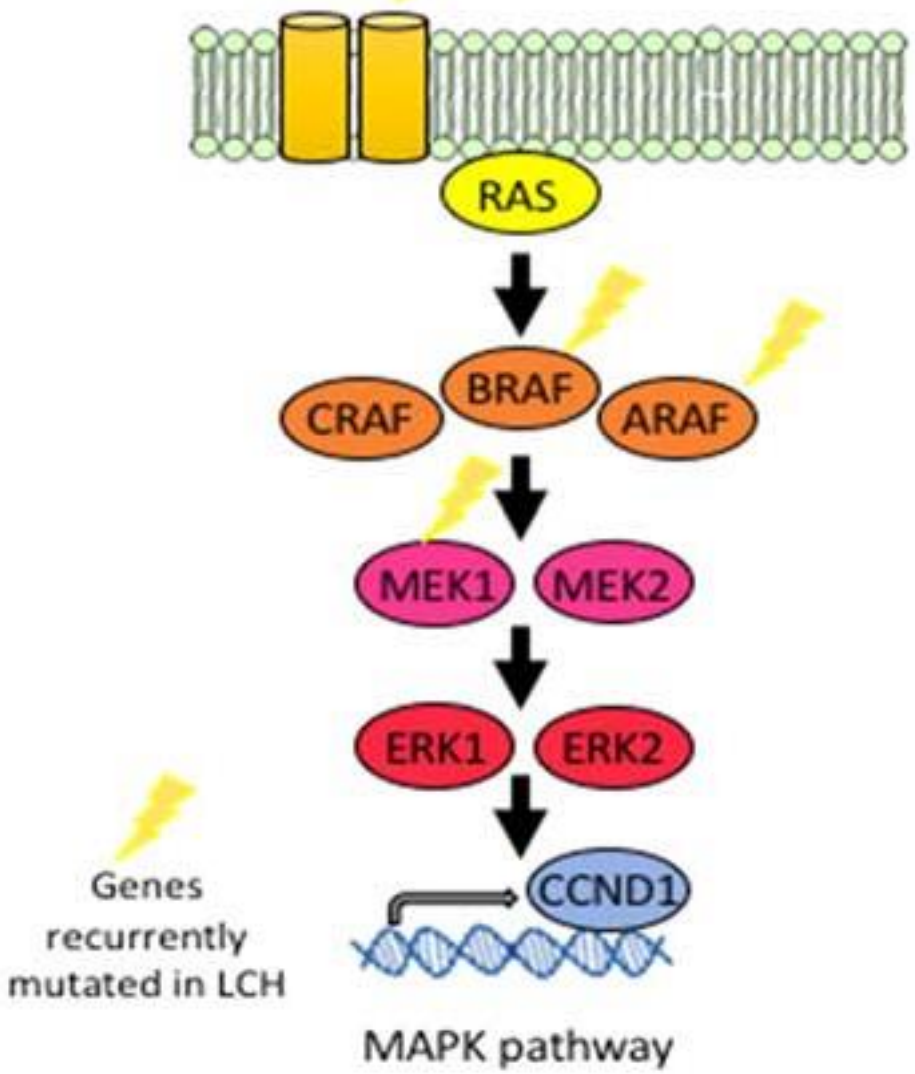


TABLE 2. Summary of Cyclin D1 Expression by Langerhans Cell Histiocytosis and Reactive/Normal Langerhans Cells

Diagnosis	Cyclin D1$^+$ (n/N [%])
Langerhans cell histiocytosis	39/39 (100)
Expression in >20% Langerhans cells	33/39 (85)
Expression in 5%-20% of Langerhans cells	6/39 (15)
Dermatopathic lymphadenitis	0/19 (0)
Dermatitis (with Langerhans cell microabscesses)	4*/18 (22)
Normal skin	0/12 (0)

*Rare, scattered CD1a$^+$ cells (5% to 10%) with cyclin D1 expression were observed.



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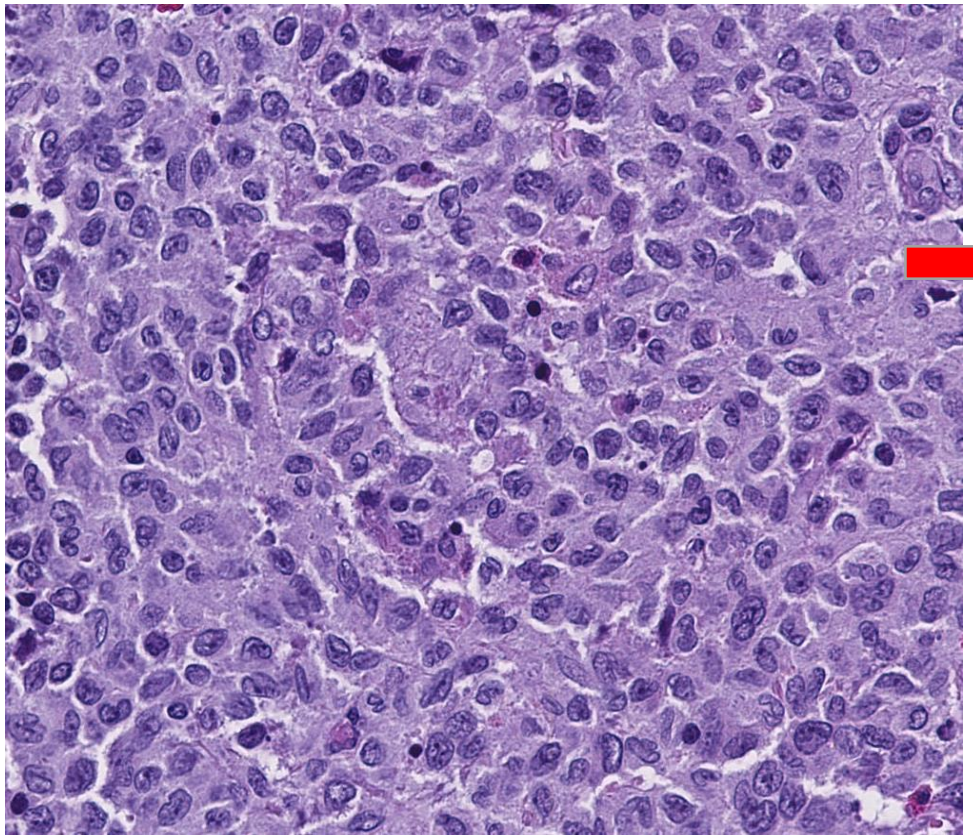
Histiocytes



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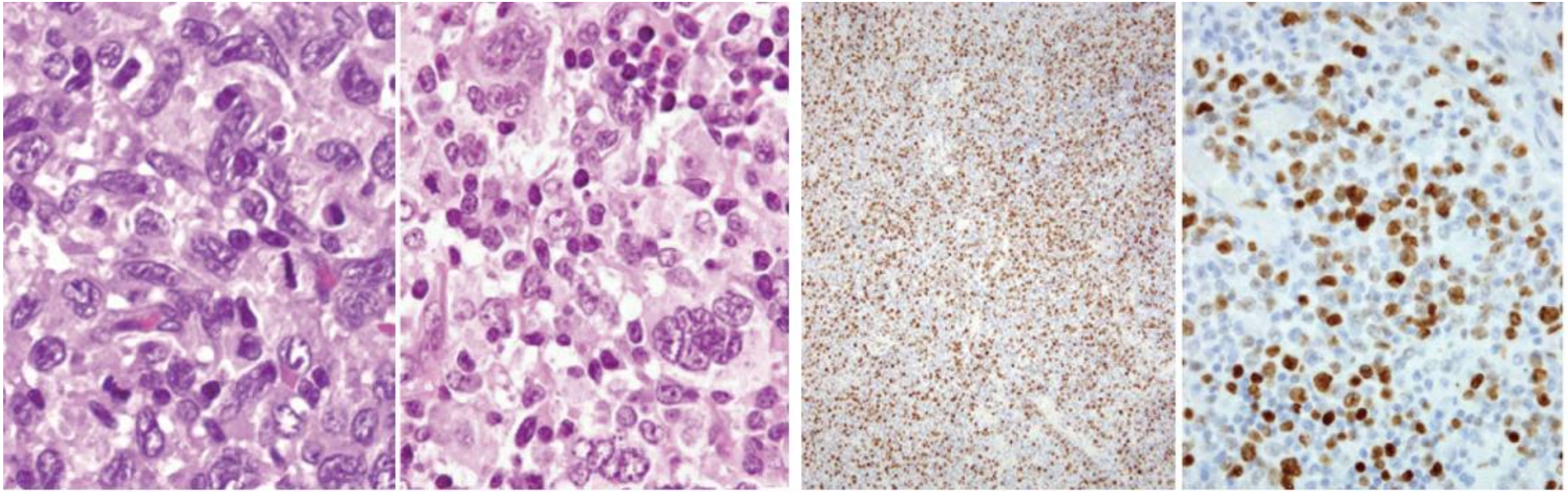
Langerhans cell histiocytic sarcoma



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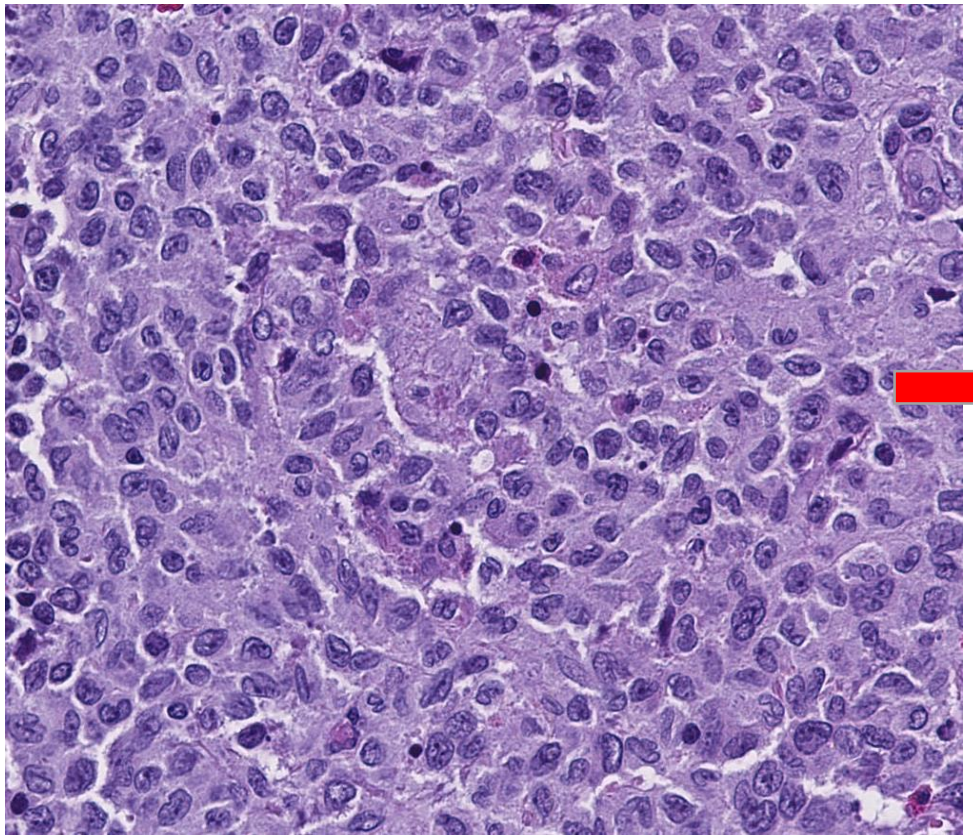
Histiocytes



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Secondary Histiocytic Neoplasm

Table 1 Reported cases of histiocytic sarcoma as a secondary malignancy.

Author	Primary diagnosis	Age at primary diagnosis (years)	Age at HS diagnosis (years)	Interval to HS (months)	FISH analysis
Brunner	FL	75	81	72	Bcl2 rearrangement
Feldman	FL	62	64	24	t(14;18)
Feldman	FL	30	42	144	t(14;18)
Feldman	FL	60	63	36	t(14;18)
Brunner	FL	75	81	72	Bcl2 rearrangement
Feldman	FL	62	64	24	t(14;18)
Feldman	FL	30	42	144	t(14;18)
Feldman	FL	60	63	36	t(14;18)
Feldman	FL	48	48	2	t(14;18)
Feldman	FL	62	62	synchronous	NR[1]
Feldman	FL	58	58	synchronous	NR[1]
Feldman	FL	67	67	7	NR[1]
Wang	FL	44	61	204	IGH/BCL2
Zeng	FL	43	47	48	t(14;18)
Feldman	B-ALL	14	16	24	NR[1]
Wang	SMZL	62	63	12	NR[1]
Castro	T-ALL	5	5	6	16p del
McClure	B-ALL	25	25	4	NR[1]
Bouabdallah	B-ALL	23	26	36	NR[1]
Castro	B-ALL	7	7	6	t(8;14)
Onciu	B-ALL	14	16	24	NR[1]
Onciu	B-ALL	13	13	3	NR[1]
Kumar	B-ALL	4	4	1	CDKN2A del
Mori	CMML	70	70	synchronous	Monocytes carrying +8 signal
Song	MGCT	16	16	8	NR[1]
Zhang	FL/DLBCL	50	50	synchronous	t(14;18)
Bassarova	FL/DLBCL	53	66	156	t(14;18)
Bassarova	DLBCL	63	64	12	t(14;18)
Shao	CLL	85	85	synchronous	13q/17p del
Hure	MCL	58	60	24	CCND1-IGH
Michonneau	HCL	48	74	312	NR[1]
Zhao	AMoL	62	62	synchronous	NR[1]
Alvaro	MALT Lymphoma	52	52	synchronous	NR[1]
Ansari	CML	69	71	30	BCR-ABL1

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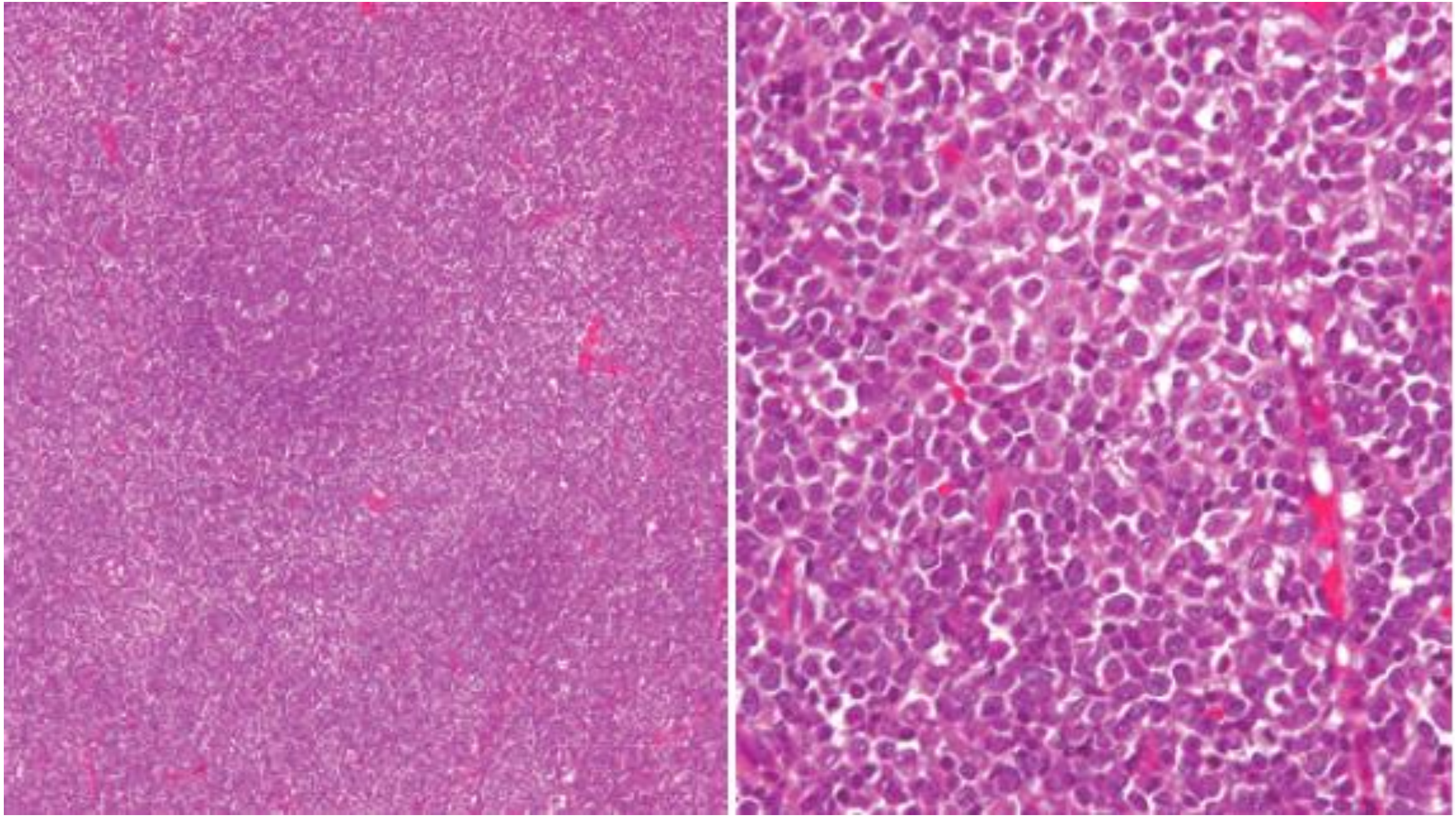
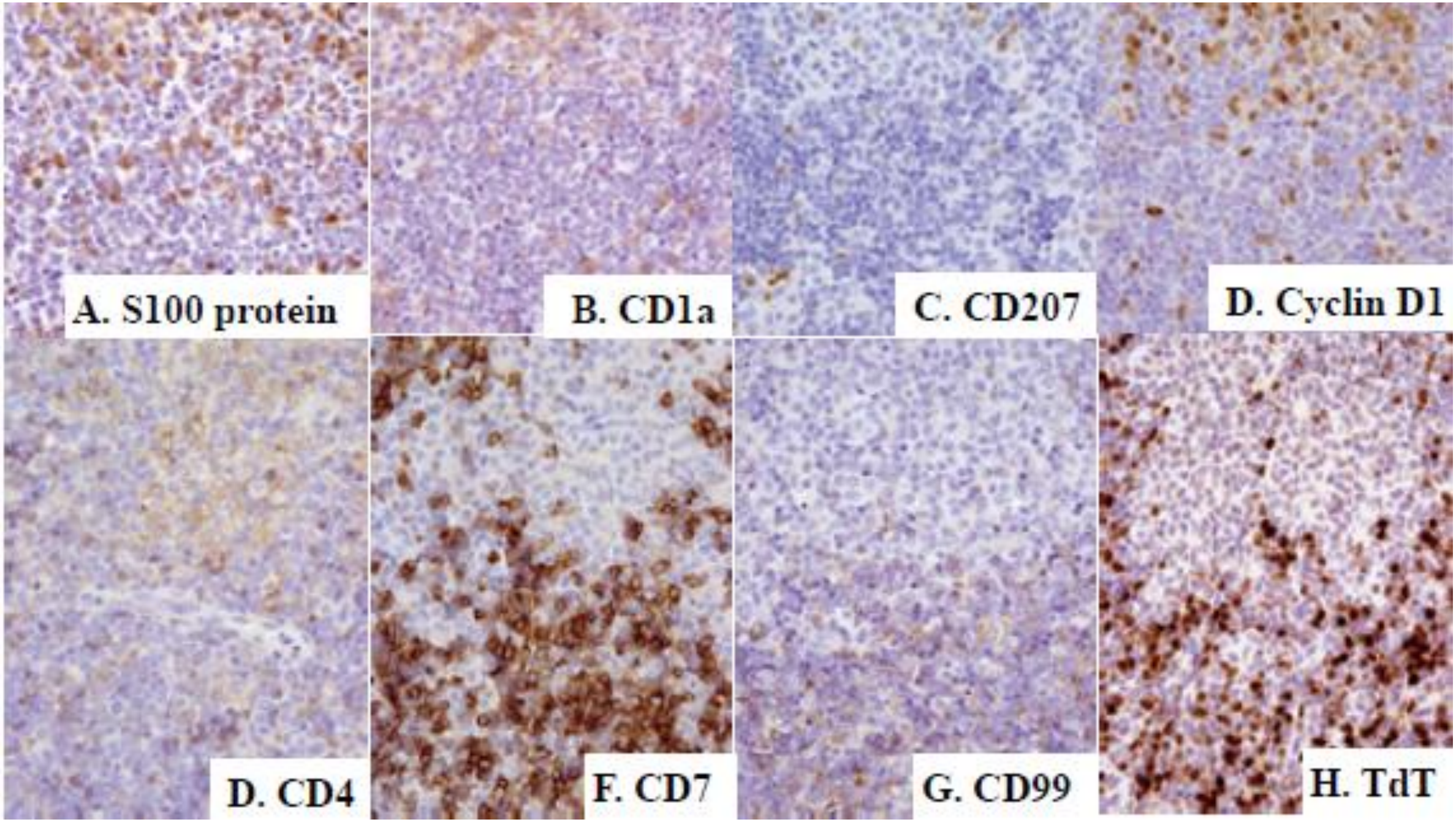
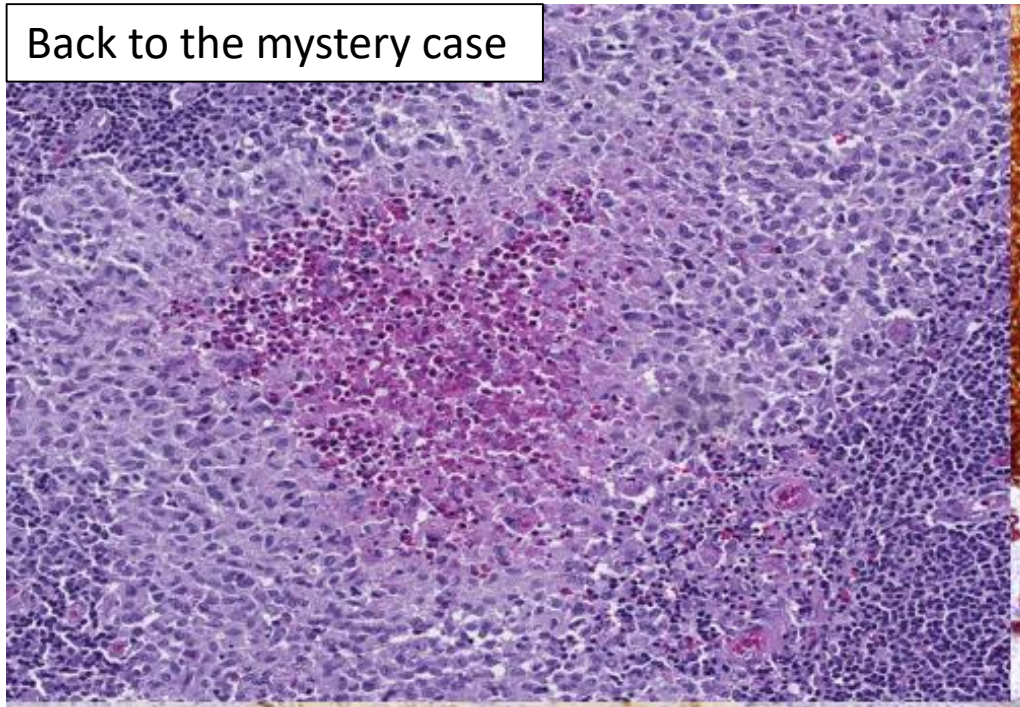
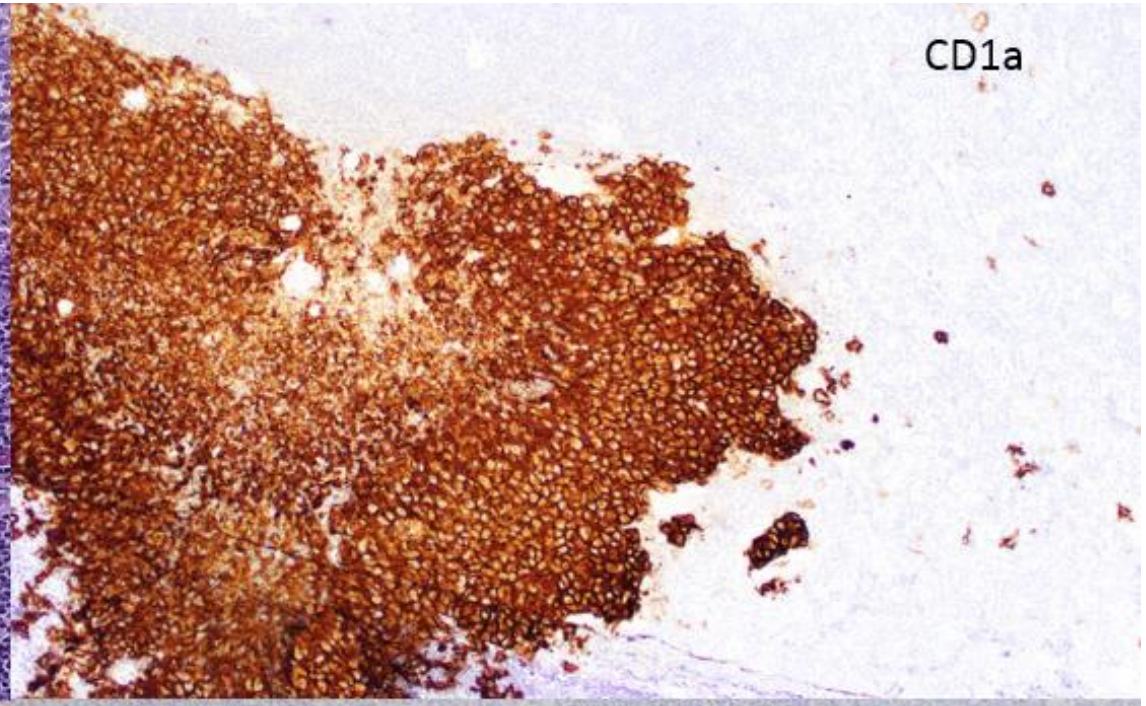
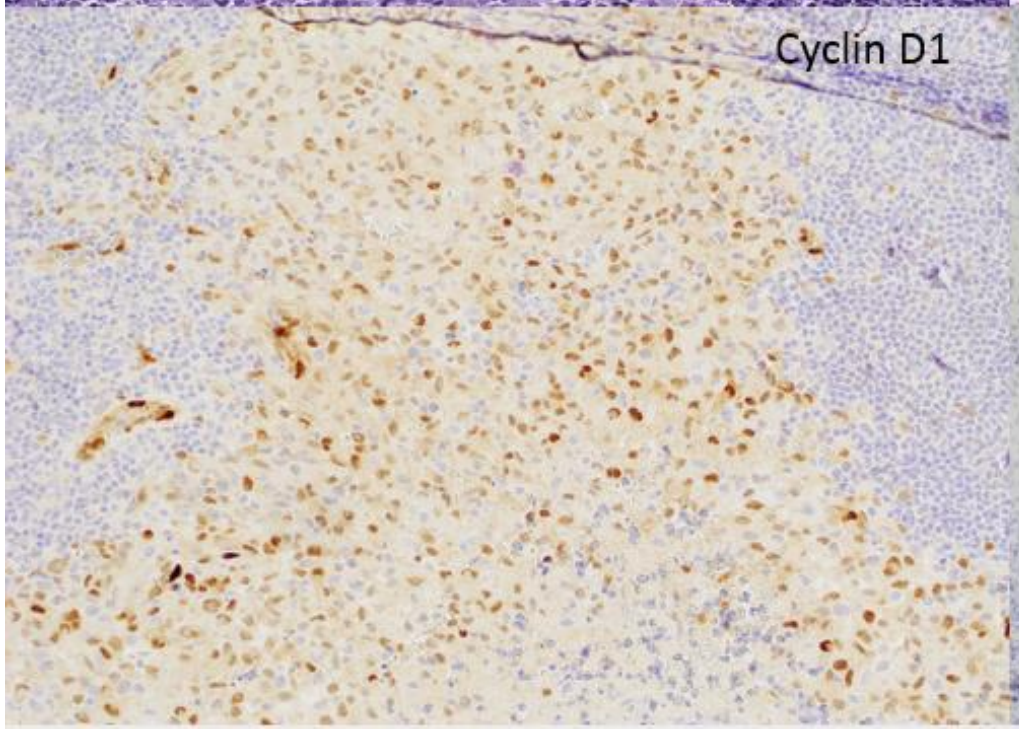


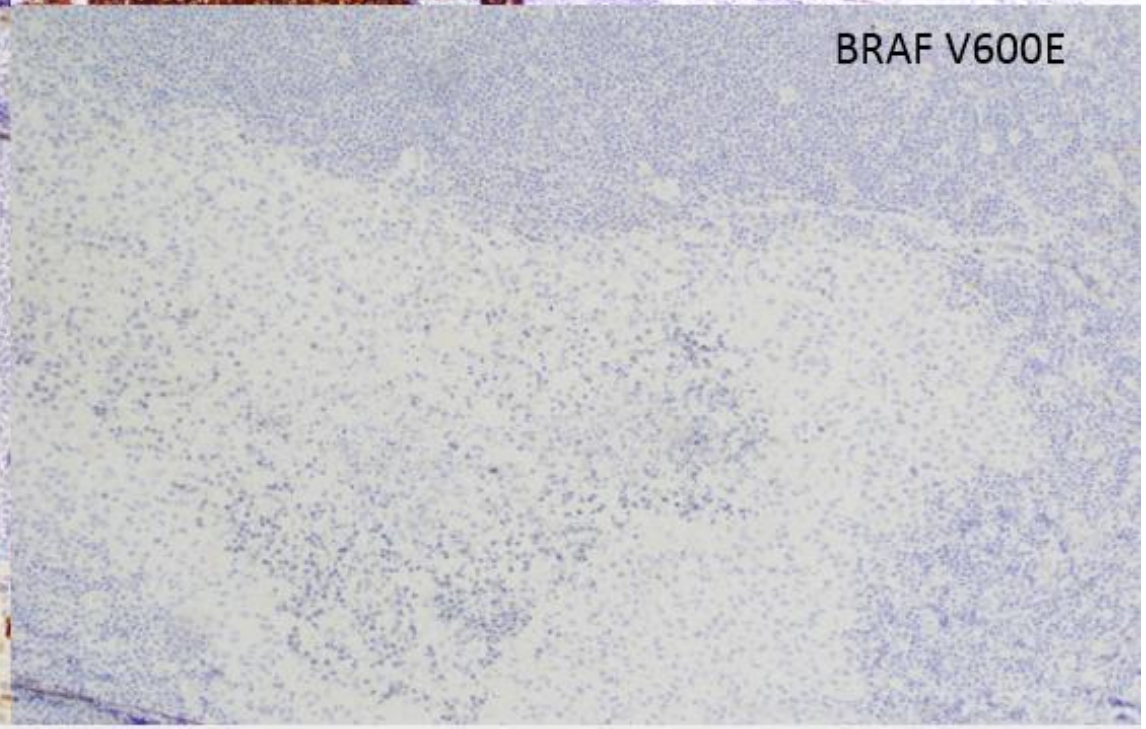

A. S100 protein
B. CD1a
C. CD207
D. Cyclin D1
D. CD4
F. CD7
G. CD99
H. TdT

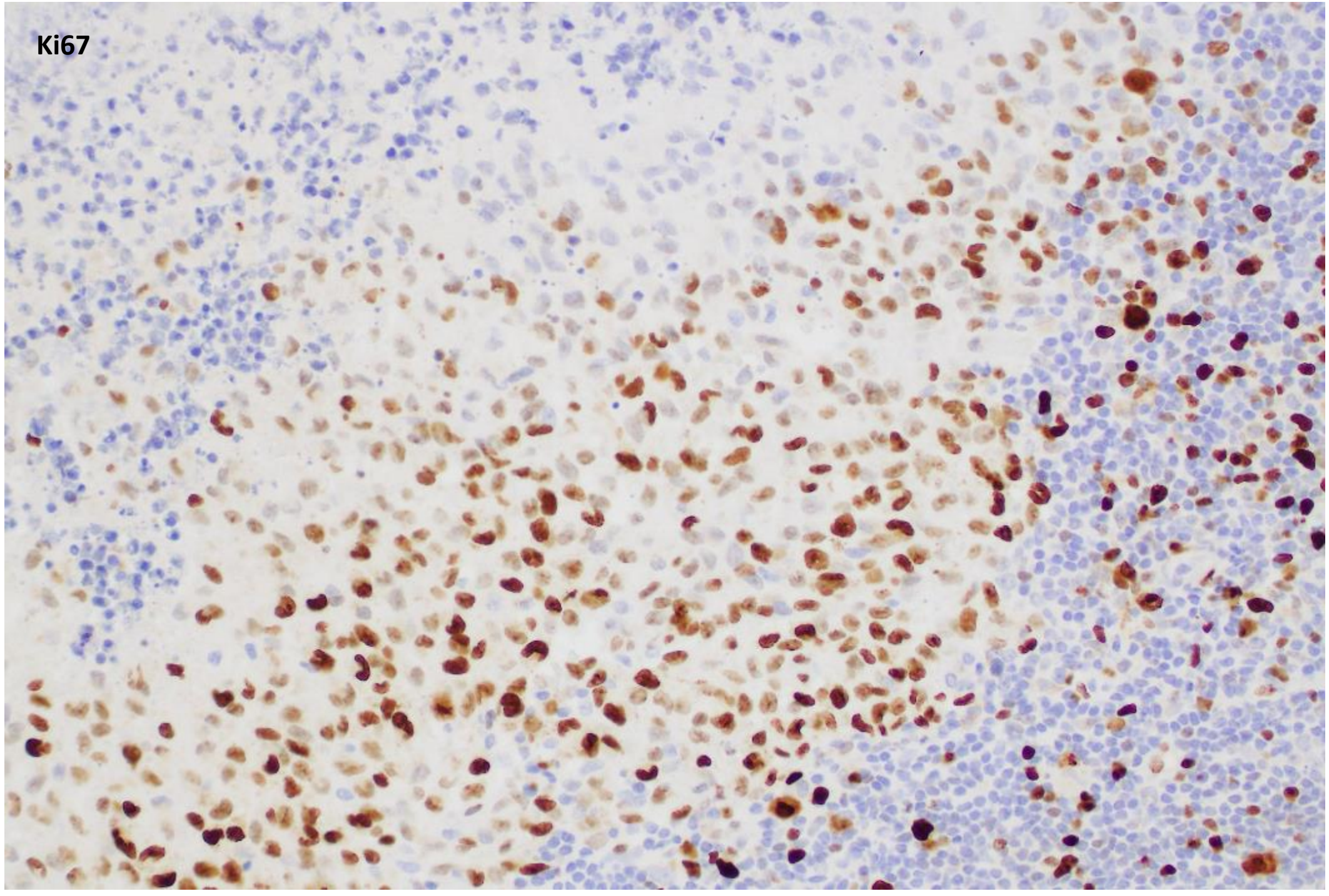
Back to the mystery case










Ki67

What's the likely diagnosis?

A- Reactive dermatopathic lymphadenopathy

B- Langerhans cell histiocytosis

C- Langerhans cell sarcoma

Morphologic atypia

Ki67 proliferation fraction

Distribution pattern

Cyclin-D1 staining

Reference

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Questions