Current Concepts in Hematopathology

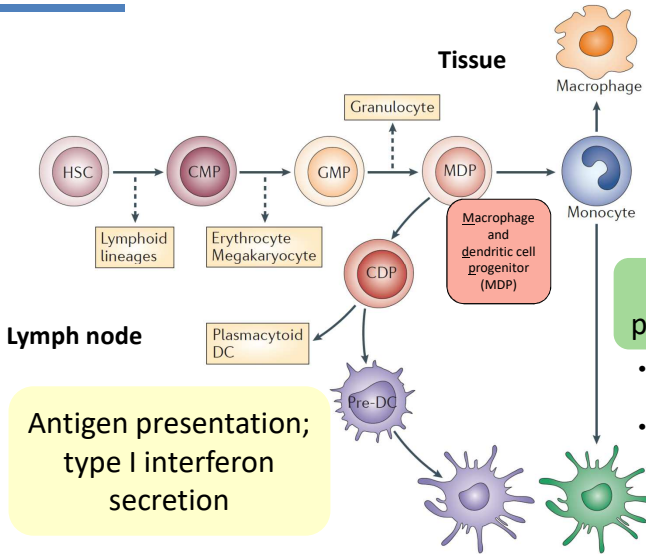
Histiocytic and Dendritic Cell Neoplasms

Elizabeth A. Morgan, MD
Associate Professor, Harvard Medical School
Brigham & Women's Hospital

Brigham and Women's Hospital
Founding Member, Mass General Brigham

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

MONONUCLEAR PHAGOCYTE SYSTEM



Phagocytic function

Peripheral blood

Antigen presentation

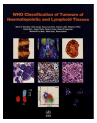
- some live in lymphoid tissues ("resident")
- some migrate to lymphoid tissues from periphery ("migratory")

Antigen presentation; type I interferon secretion

- Langerhans cells (skin/mucosa → migrate to LNs)
- Interdigitating dendritic cells
- Indeterminate cell

McClain K et al. *Nat Rev Dis Prim*. 2021;7: 73.
Chow A et al. *Nat Rev Immunol*. 2011;11: 788-798.

WHO CLASSIFICATION: HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS



4th revised edition (published 2016)

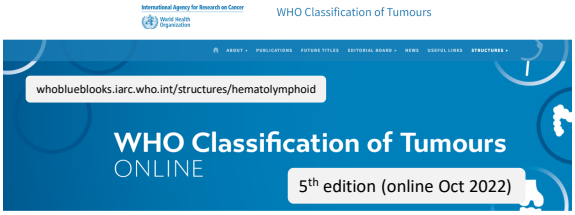
CHAPTER 17

Histiocytic and dendritic cell neoplasms

Histiocytic sarcoma
Tumours derived from Langerhans cells
Indeterminate dendritic cell tumour
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumour
Disseminated juvenile xanthogranuloma
Erdheim–Chester disease

CHAPTER 9

Blastic plasmacytoid dendritic cell neoplasm



Haematolymphoid

Histiocytic/Dendritic cell neoplasms

Plasmacytoid dendritic cell neoplasms
Plasmacytoid dendritic cell neoplasms
Mature plasmacytoid dendritic cell proliferation
Blastic plasmacytoid dendritic cell neoplasm

Langerhans cell neoplasms
Langerhans cells neoplasms
Langerhans cell histiocytosis
Langerhans cell sarcoma

Histiocyte/macrophage neoplasms
Histiocytic neoplasms
Juvenile xanthogranuloma
Erdheim-Chester disease
Rosai-Dorfman Disease
ALK related histiocytosis
Histiocytic sarcoma

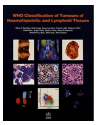
Interdigitating dendritic cell
Interdigitating dendritic cell neoplasms
Indeterminate dendritic cell tumour
Interdigitating dendritic cell sarcoma

Lymphoid tissue stroma-derived neoplasms

Mesenchymal dendritic cell neoplasms
Follicular dendritic cell neoplasms
Follicular dendritic cell sarcoma
Inflammatory EBV+ follicular dendritic cell sarcoma
Fibroblastic reticular cell tumour

Splenic stromal tumours
Littoral cell angioma
Littoral cell angioma

WHO CLASSIFICATION: HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

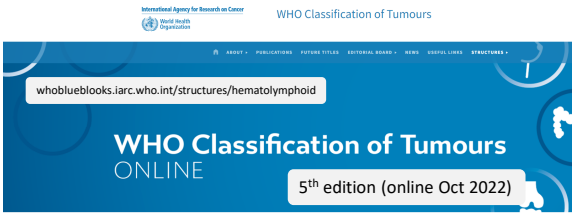


4th revised edition (published 2016)

CHAPTER 17

Histiocytic and dendritic cell neoplasms

Histiocytic sarcoma
Tumours derived from Langerhans cells
Indeterminate dendritic cell tumour
Interdigitating dendritic cell sarcoma
Disseminated juvenile xanthogranuloma
Erdheim–Chester disease



Haematolymphoid

Histiocytic/Dendritic cell neoplasms

Langerhans cell neoplasms
Langerhans cells neoplasms
Langerhans cell histiocytosis
Langerhans cell sarcoma

Histiocyte/macrophage neoplasms
Histiocytic neoplasms
Juvenile xanthogranuloma
Erdheim-Chester disease
Rosai-Dorfman Disease
ALK related histiocytosis
Histiocytic sarcoma

Interdigitating dendritic cell
Interdigitating dendritic cell neoplasms
Indeterminate dendritic cell tumour
Interdigitating dendritic cell sarcoma

HISTIOCYTOSES/NEOPLASMS OF THE MACROPHAGE-DENDRITIC CELL LINEAGE

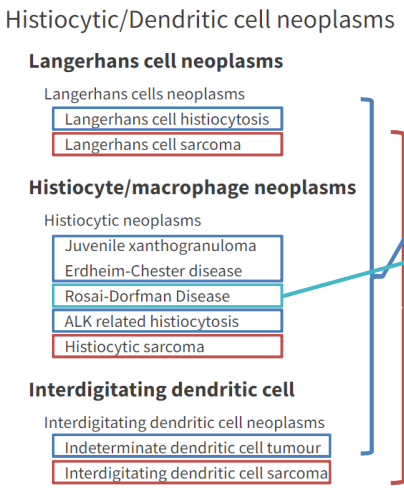
Revised classification published in 2016 by the Histiocyte Society

Group	Entities
L	Langerhans cell histiocytosis (LCH) Indeterminate cell histiocytosis Erdheim-Chester disease (ECD) Mixed ECD and LCH
C	Cutaneous non-LCH histiocytoses Cutaneous non-LCH histiocytoses with a major systemic component
M	Primary malignant histiocytosis Secondary malignant histiocytosis
R	Familial Rosai-Dorfman disease (RDD) Classical (nodal) RDD Extranodal RDD Neoplasia-associated RDD Immune disease–associated RDD Other non-C, non-L, non-M, and non-H histiocytoses
H	Primary HLH: Mendelian-inherited conditions leading to HLH Secondary HLH (apparently non-Mendelian HLH) HLH of unknown/uncertain origin

HLH = hemophagocytic lymphohistiocytosis

Emile JF et al. *Blood*. 2016;127(22): 2672-2681.
Frater JL. *Blood*. 2016;127(22): 2655-2656.

COMPARISON OF CLASSIFICATION SCHEMES



Group	Entities
L	Langerhans cell histiocytosis (LCH) Indeterminate cell histiocytosis Erdheim-Chester disease (ECD) Mixed ECD and LCH
C	Cutaneous non-LCH histiocytoses Cutaneous non-LCH histiocytoses with a major systemic component
M	Primary malignant histiocytosis Secondary malignant histiocytosis
R	Familial Rosai-Dorfman disease (RDD) Classical (nodal) RDD Extranodal RDD Neoplasia-associated RDD Immune disease–associated RDD Other non-C, non-L, non-M, and non-H histiocytoses
H	Primary HLH: Mendelian-inherited conditions leading to HLH Secondary HLH (apparently non-Mendelian HLH) HLH of unknown/uncertain origin

Frater JL. *Blood*. 2016;127(22): 2655-2656.

LANGERHANS CELL HISTIOCYTOSIS

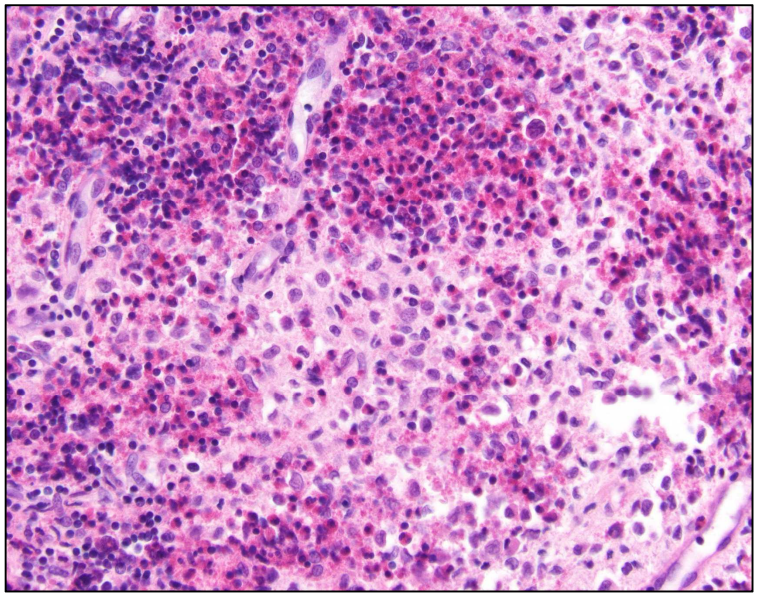
Definition

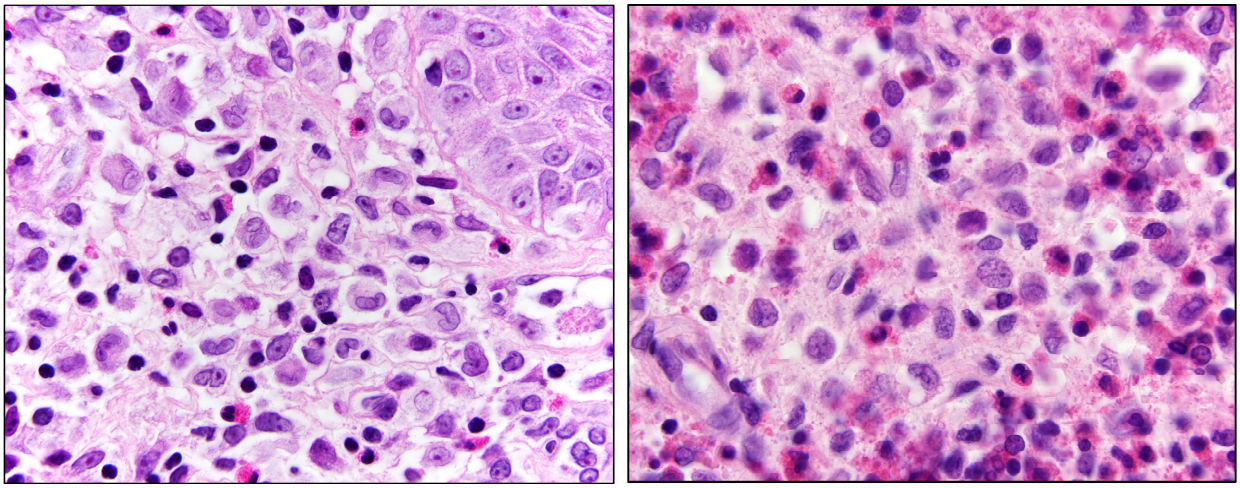
- proliferation of dendritic cells with the same immunophenotype as specialized dendritic cells - “epidermal Langerhans cells” - found in the skin and mucosa
- may affect any anatomic site
  - single or multifocal (confined to an organ system, particularly bone, especially in children)
  - disseminated disease can include wide range of anatomic sites including skin (40%)
- may be associated with diabetes insipidus

LANGERHANS CELL HISTIOCYTOSIS

Morphology

- large, oval cells with grooved nuclei and dispersed chromatin
- do not display dendritic processes
- background of (often abundant) small lymphocytes, eosinophils macrophages, multinucleated giant cells > neutrophils, plasma cells
- lesional cells may be sparse in later lesions
- shows sinusoidal pattern in LN

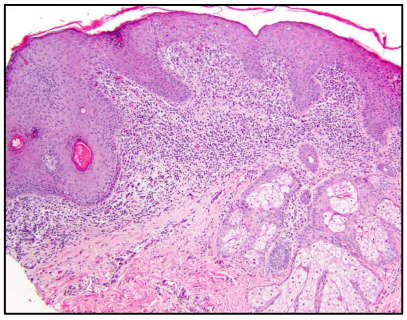


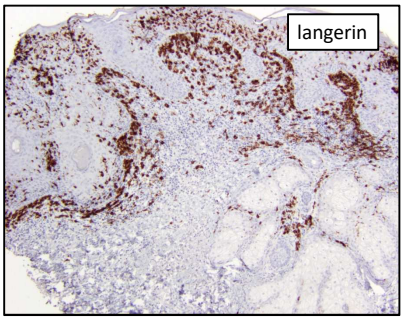


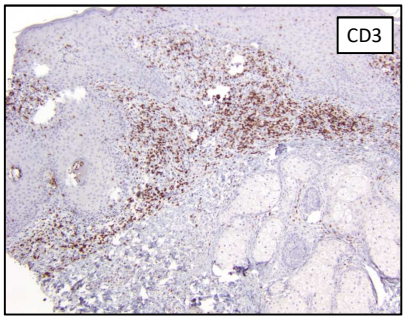
LANGERHANS CELL HISTIOCYTOSIS

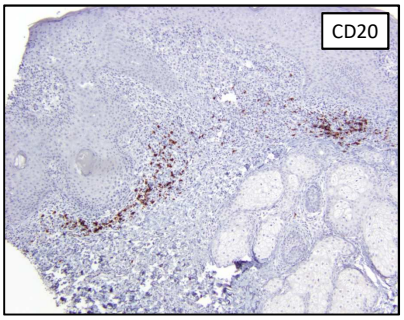
Immunophenotype

- "Langerhans cell" markers
  - S100+ (nuclear and cytoplasmic)
  - CD1a+
  - langerin (CD207)+
- "macrophage" markers
  - CD68 -/+, CD163 -
  - lysozyme weak to negative (but admixed macrophages will be strongly positive)



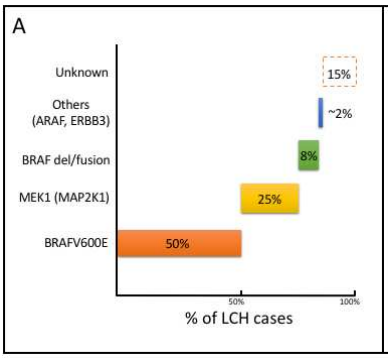


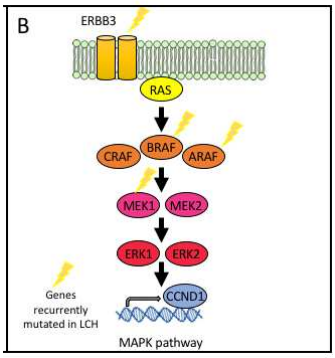




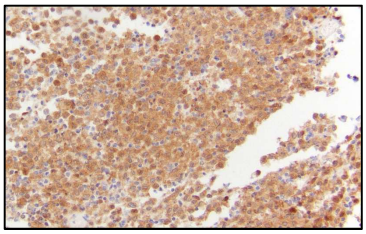
LANGERHANS CELL HISTIOCYTOSIS

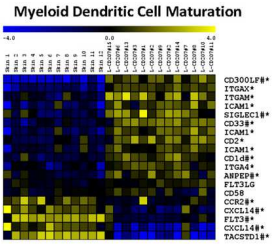
Genetics/cell-of-origin





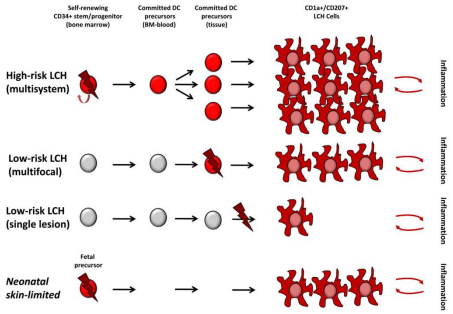
BRAF V600E mutation-specific antibody





Gene expression profiling suggests that LCH cells are derived from bone marrow-derived immature myeloid dendritic cells

"Misguided myeloid dendritic cell" model

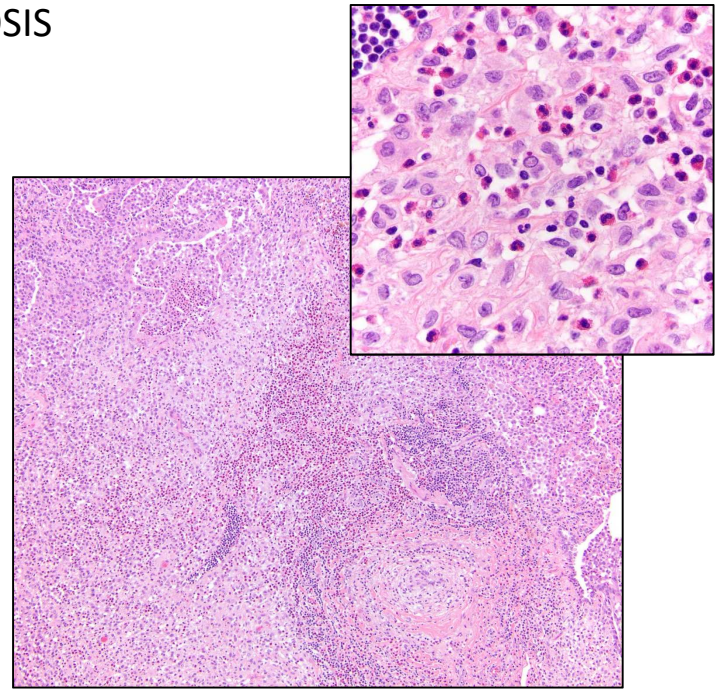


Allen CE et al. *J Immunol*. 2010;184:4557-4567.
Collin M et al. *Hematol Oncol Clin North Am*. 2015;29(5): 825–838.
Shanmugam V et al. *Am J Surg Pathol*. 2017 Oct;41(10):1390-1396.

LANGERHANS CELL HISTIOCYTOSIS

Pulmonary LCH

- >90% in young or ex-smokers
- peak incidence between 20 and 40 years
- granulomas form around small airways and can be destructive/cause tissue remodeling
- composed of Langerhans cells with the same immunophenotype as LCH at other sites
- debate: reactive, clonal or neoplastic?
  - unpredictable clinical course
    - may resolve with smoking cessation
    - may require therapeutic intervention
  - recurrent genetic abnormalities
    - *BRAF V600E* (30-50%)
    - *MAP2K1* mutations (mutually exclusive with *BRAF* mutations)

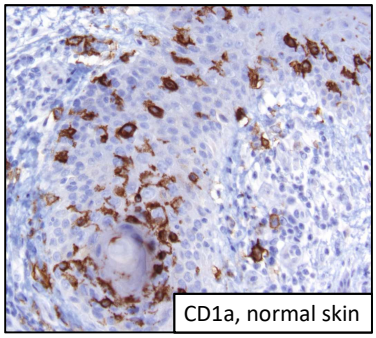


Vassallo R et al. *Thorax*. 2017;72:937–945.

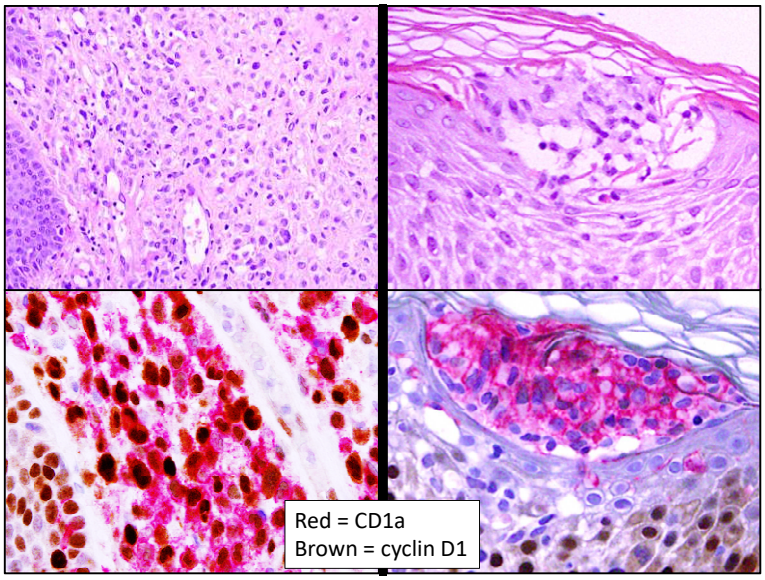
LANGERHANS CELL HISTIOCYTOSIS

Differential diagnosis

- reactive Langerhans cell collections
- indeterminate dendritic cell tumor
- Langerhans cell sarcoma



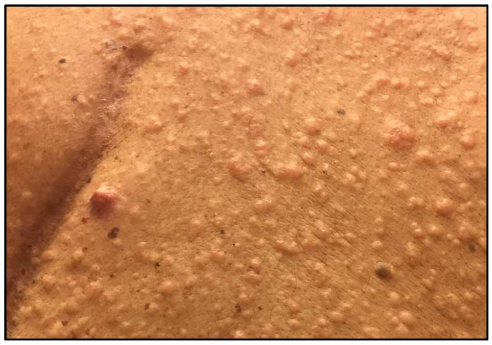
reactive Langerhans cells have dendritic processes (best seen on CD1a IHC)



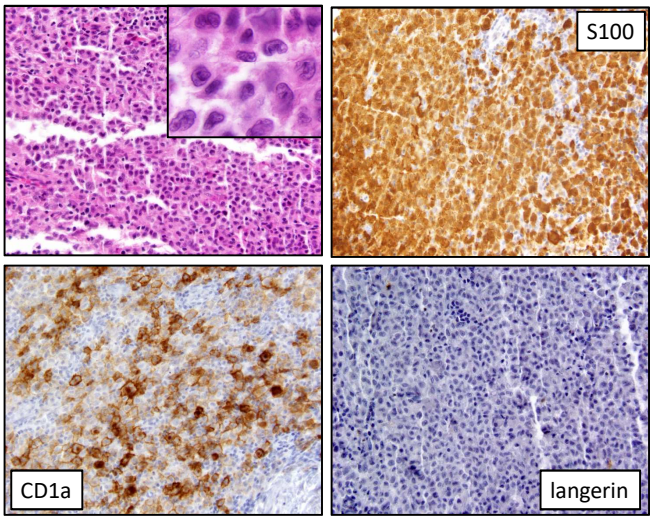
Shanmugam V et al. *Am J Surg Pathol.* 2017 Oct;41(10):1390-1396.

INDETERMINATE DENDRITIC CELL TUMOR

- extraordinarily rare
- involves dermis; may extend to subcutis
- multiple generalized papules, nodules or plaques
- cells resemble Langerhans cells morphologically
- S100+, CD1a+; langerin-negative
- no Birbeck granules on EM
- may have *BRAF V600E* mutation
- few cases *with ETV3-NCOA2* translocation



Clinical image courtesy of Dr. Mackenzie Asel



ERDHEIM-CHESTER DISEASE

Clinical features

no LN involvement, in contrast to LCH

- adults, M>F
- bilateral, symmetric osteosclerotic lesions (95%)
- may also involve extraskeletal tissues
  - restrictive pericarditis
  - perinephric fibrosis
  - yellow plaques (commonly eyelids/periorbital): xanthelasma
  - central diabetes insipidus
- variable clinical outcomes: indolent to life-threatening
- high prevalence of concomitant myeloid neoplasms → bmbx recommended, esp in setting of unexplained CBC abnormalities
- diagnosis requires clinicopathologic and radiologic correlation

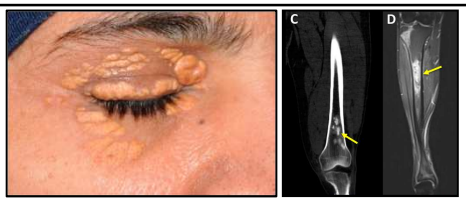
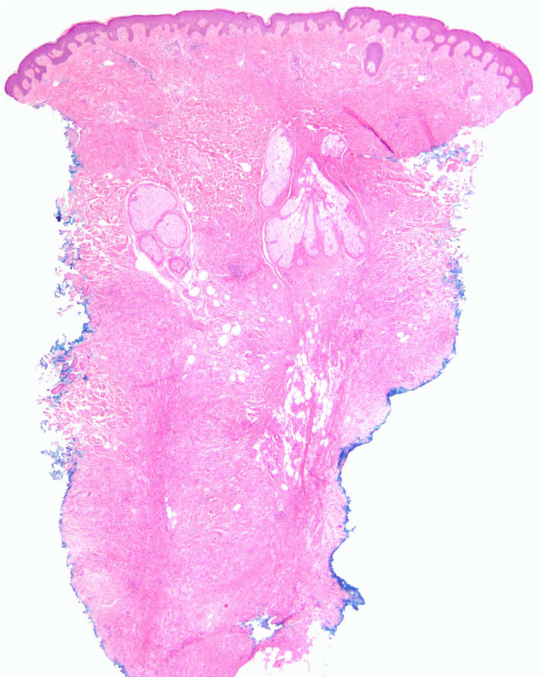


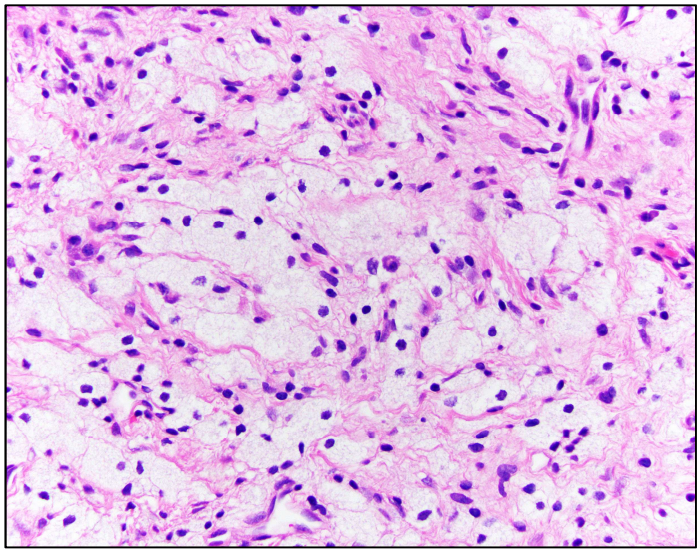
Table 2. ECD organ involvement in NIH patients and in the literature

Organ system and clinical findings	NIH patients,* n (%)	Veyssier-Belot et al† (%)	Haroche et al‡ (%)
Bone	57 (95)	NR	96
Kidney	39 (65)	27	68
Periaortic encasement	37 (62)	NR	66
Hypogonadism	36 (60)	NR	NR
Lung	31 (52)	14	43
Bone pain	28 (47)	47	40
Maxilla and mandible§	24 (47)	NR	NR
Diabetes insipidus	28 (47)	29	25
CNS disease infiltration	23 (38)	17	51
Retro-orbital area ± exophthalmos	15 (27)	29	25
Heart (pseudotumor in RA)	22 (37)	NR	19
Xanthelasma	20 (33)	19	28
Skin	15 (25)	10	NR
Pericardial disease	5 (8)	7	42

Goyal G et al. *Blood*. 2020; 135(22):1929-45.
Chasset F et al. *Am J Acad Dermatol*. 2016;74:513-20.

Diamond EL et al. *Blood*. 2014;124(4):483-492.
Estrada-Veras JI. *Blood Adv*. 2017;1(6): 357-66.





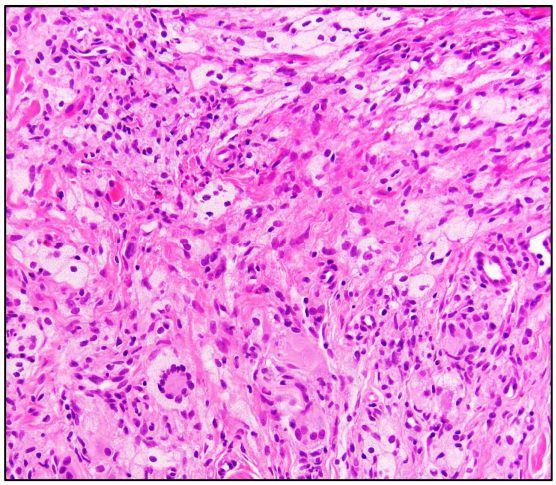
ERDHEIM-CHESTER DISEASE

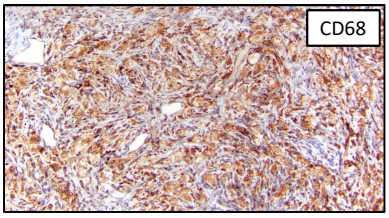
Morphology & immunophenotype

- Classic:
  - sheets of foamy macrophages/ xanthogranulomatous infiltrates
  - multinucleated Touton cells
  - fibrosis
  - mixed inflammatory cells: lymphocytes/plasma cells > neutrophils
- Atypical:
  - florid lymphohistiocytic infiltrates
  - fibrosis with scattered foamy histiocytes and rare/absent Touton giant cells

- PU.1+, CD68+, CD163+, lysozyme+, fascin+
- CD1a-negative, Langerin-negative
- 20-30% weak/focal S100 expression

may be difficult/impossible to distinguish from reactive xanthomatous macrophages in the setting of chronic inflammatory conditions based solely on histologic/immunophenotypic features



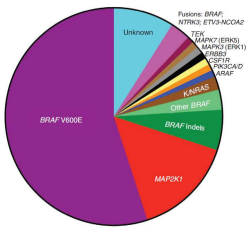


Chasset F et al. *Am J Acad Dermatol*. 2016;74:513-20.

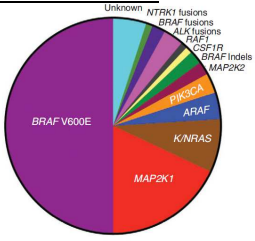
ERDHEIM-CHESTER DISEASE

Genetics

Similar genetic lesions in LCH and ECD



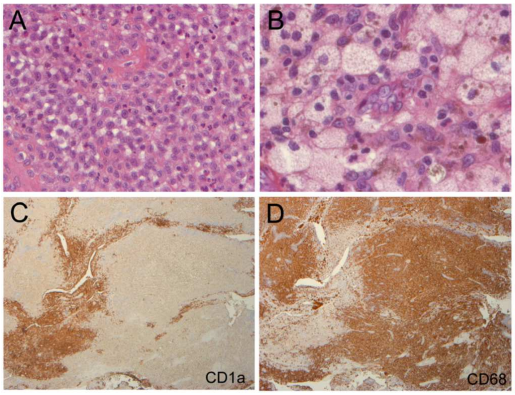
Langerhans cell histiocytosis



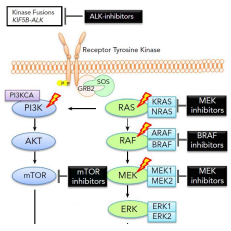
* A proportion of *PIK3CA* mutant patients have concomitant *BRAF*V600E mutations.

Erdheim-Chester disease

Up to 20% of ECD pts also have LCH at same or different site



- molecular testing is recommended for ECD
  - may help increase confidence in diagnosis if atypical histologic features or absence of osseous lesions
  - may identify target for therapeutic intervention
- strong BRAF IHC expression may be helpful in absence of molecular findings



Chakraborty R et al. *Cold Spring Harb Perspect Med*. 2021 May 3;11(5):a034892.
Goyal G et al. *Blood*. 2020; 135(22):1929-45.
Hervier B et al. *Blood*. 2014;124(7):1119-1126.
Emile JF et al. *Blood*. 2016;127(22): 2672-2681.

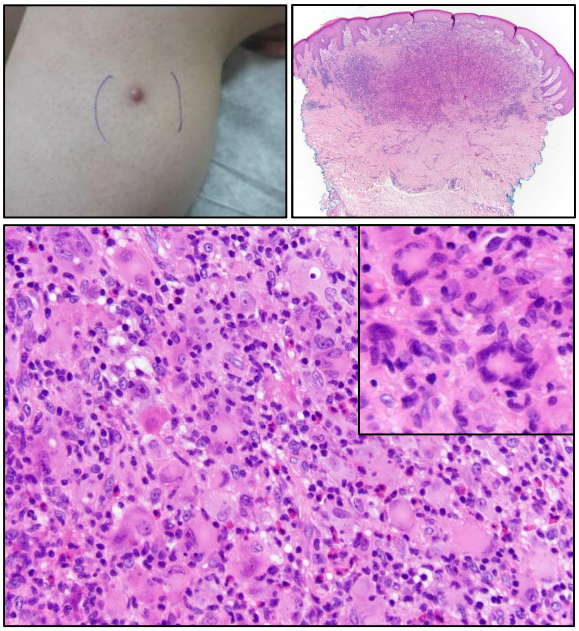
JUVENILE XANTHOGRANULOMA

Most cases:

- solitary or several red-yellow papules/nodules
- resembles dermatofibroma or Spitz nevus
- well-circumscribed nodule
- epidermal collarette
- histiocytes/foamy cells, Touton giant cells, lymphocytes, eosinophils
- Positive for CD68, CD163; negative CD1a, langerin
- may contain S100+ cells with emperipolesis
- most skin-only cases do not have underlying mutations, although may be associated with NF1
- benign outcome: may resolve spontaneously

Disseminated/systemic form (~5%)

- typically infant to 10 years old; may occur in adults
- can involve mucosal surfaces, CNS, dura, pituitary stalk, eye, liver, lung, LN and BM; potential for morbidity and mortality
- challenging area for classification (await 2022 WHO)
  - recurrent *BRAFV600E*, *NTRK1* fusions and mutations in *MAP2K1* and *CSF1R*
  - "consider as ECD all extracutaneous or disseminated JXG with gain-of-function mutation of *BRAF*, *NRAS*, *KRAS*, or *MAP2K1*" (Emile JF et al. *Blood*. 2016;127(22): 2672-2681.)
  - *BRAFV600E* "positive cases should be strongly favored to be in ECD family" (Goyal G et al. *Blood*. 2020; 135(22):1929-45.)



Clinical image courtesy of Dr. Geoffrey Yang

ALK-RELATED HISTIOCYTOSIS

Modern Pathology (2019) 32:598–608
https://doi.org/10.1038/s41379-018-0168-6

USCAP

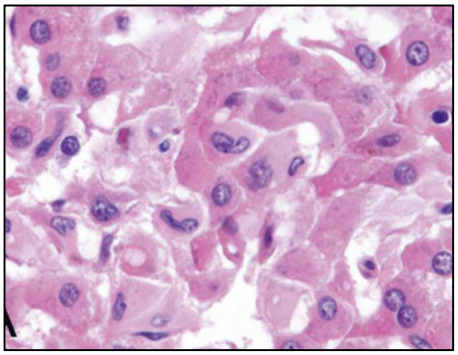
ARTICLE

ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of *KIF5B-ALK* fusion

Kenneth Tou En Chang[1,2] · Amos Zhi En Tay[1] · Chik Hong Kuick[1] · Huiyi Chen[1] · Elizabeth Algar[3,4] · Nadine Taubenheim[3] · Janine Campbell[5] · Francoise Mechinaud[6] · Martin Campbell[6] · Leanne Super[6] · Chavit Chantranuwat[7] · S. T. Yuen[8] · John K. C. Chan[9] · Chung W. Chow[10,11]

10 cases

- 6 disseminated (infant to toddler at presentation; 5 of 6 with eventual disease resolution)
- 4 localized (nasal skin, foot, breast, and intracranial cavernous sinus - surgical resection or crizotinib)
- large cells with irregularly folded nuclei, fine chromatin, and abundant eosinophilic cytoplasm +/- emperipolesis
- typically not xanthomatous
  - positive for ALK1, CD68, CD163; +/- S100; negative for CD1a, Langerin
- features resembling JXG (foamy histiocytes, Touton giant cells) may arise over time
- *KIF5B-ALK* fusion (n=5), *COL1A2-ALK* (n=1); no correlation with anatomic distribution



- authors propose that ALK-positive histiocytosis likely represents a distinct clinicopathologic entity
  - should the few prior cases of JXG and ECD with ALK fusions be classified as ALK-positive (ALK-related) histiocytosis?
  - await 2022 WHO classification
- recommend performing ALK1 IHC on all atypical histiocytic proliferations → may provide a therapeutic option (regardless of histologic classification)

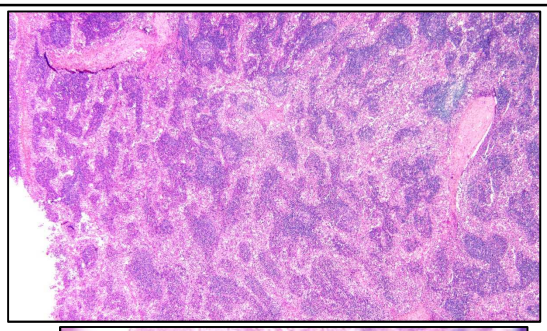
ROSAI-DORFMAN DISEASE

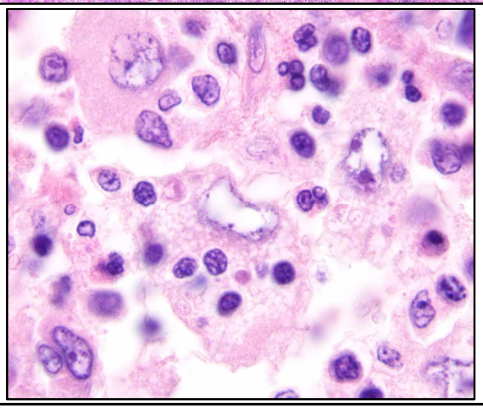
Clinical & morphologic features

- painless, massive lymphadenopathy
- fever, night sweats, weight loss, fatigue
- elevated ESR, polyclonal hypergammaglobulinemia
- ~40% of cases with extranodal involvement

- large histiocytic cells with emperipolesis
- lymphocytes, plasma cells, neutrophils, non-RD histiocytes
- eosinophils typically not seen
- may see increased IgG4+plasma cells → systemic evaluation for associated IgG4-related disease recommended if IgG:IgG4 >40%
- other histiocytoses may show occasional emperipolesis (JXG; LCH/sarcoma; HS)

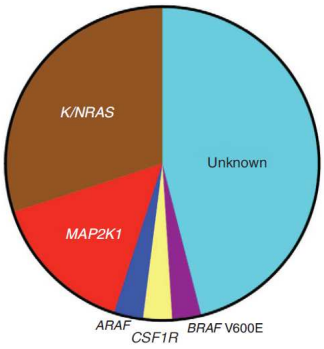
- positive for CD68, CD163, PU.1, fascin, lysozyme, factor XIIIa
- positive for S100
- positive for cyclin D1 and pERK (active MAPK–ERK pathway)
- negative for CD1a and langerin (CD207)





ROSAI-DORFMAN DISEASE

Genetics



Rosai–Dorfman–Destombes disease

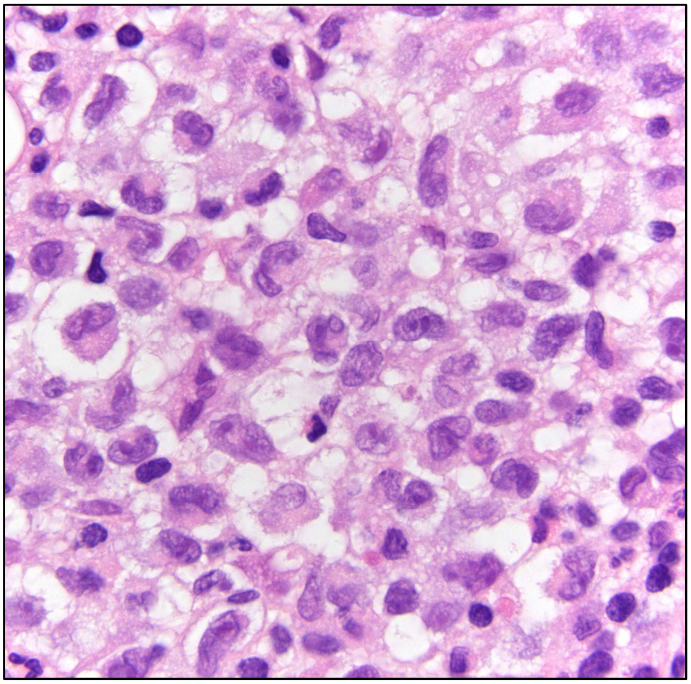
- etiology is unknown
- mutations have been identified but at an overall frequency much lower than in LCH, ECD and JXG
- no correlation between mutational status and clinical outcome

Chakraborty R et al. *Cold Spring Harb Perspect Med*. 2021 May 3;11(5):a034892.
Diamond EL et al. *Cancer Discov*. 2015. 6(2); 1–12.

HISTIOCYTIC SARCOMA

Clinical features

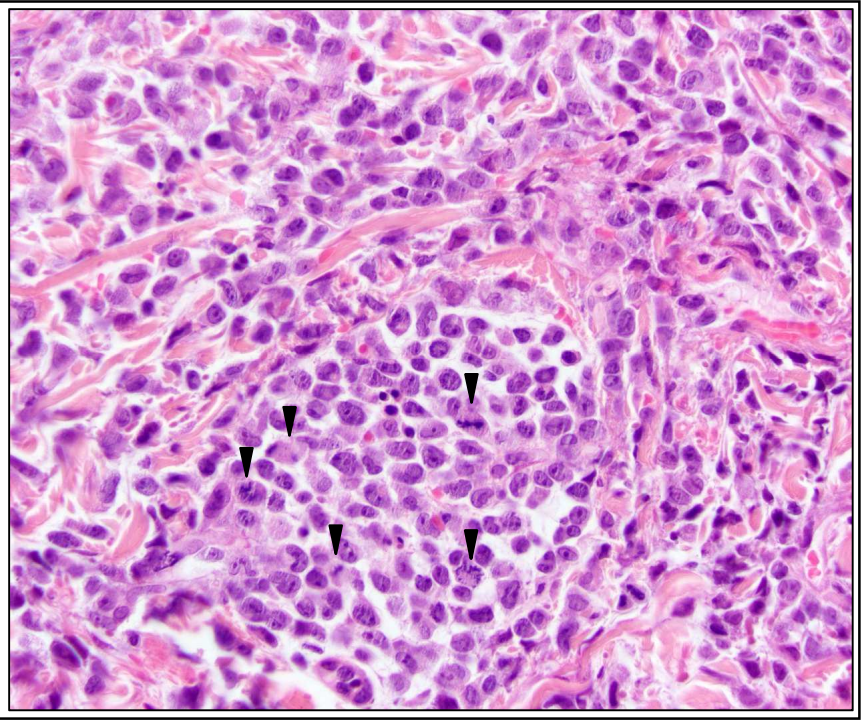
- rare, aggressive, adults
- malignant proliferation of cells with features of tissue histiocytes
- often extranodal tissues, including skin
- may arise in patients with mediastinal germ cell tumors (typically malignant teratoma)
- may arise in patients with other hematopoietic neoplasm, especially lymphoma or acute lymphoblastic leukemia



HISTIOCYTIC SARCOMA

Morphology

- sheets of large cells with pleomorphic nuclei and abundant eosinophilic cytoplasm
- typically non-cohesive but may have sinusoidal distribution in LN, spleen, liver
- frequent mitoses
- variable inflammatory background (may obscure neoplastic cells, particularly in CNS)



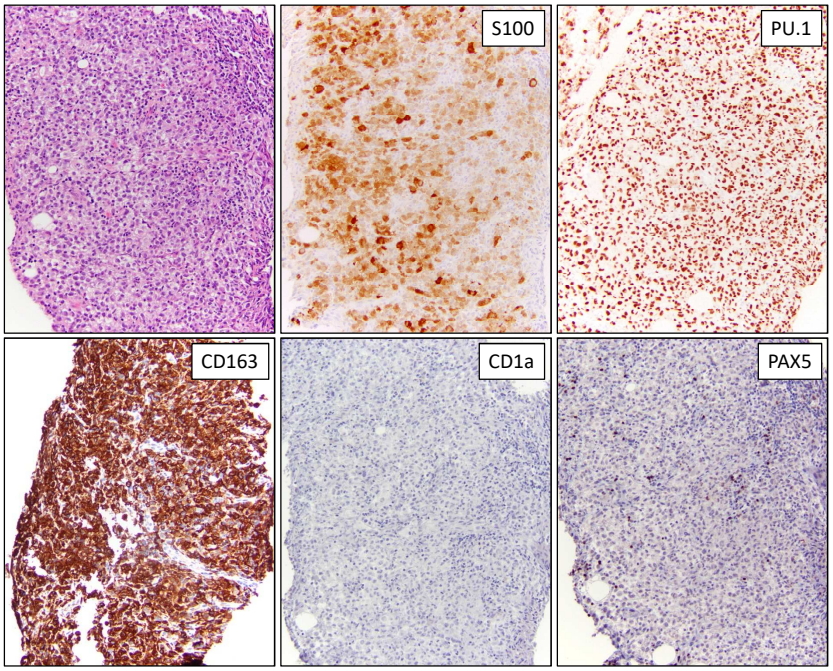
HISTIOCYTIC SARCOMA

Immunophenotype

- CD45+
- CD68+, CD163+, lysozyme+, PU.1+
- S100-/+
- CD1a-, langerin-
- MPO-
- B and T-lineage-
- HMB45-
- CD21-, CD35-

Differential diagnosis

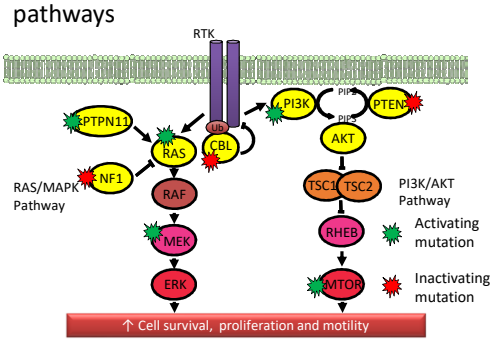
- B- or T-cell lymphoma with pleomorphic morphology (particularly anaplastic large cell lymphoma)
- myeloid sarcoma
- other more common S100+ disorders: melanoma, LCH



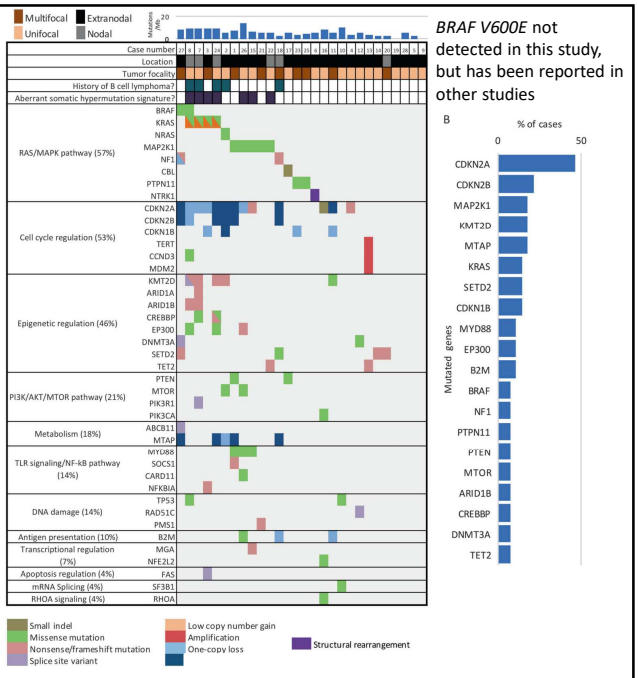
HISTIOCYTIC SARCOMA

Genetics

- recurrent activating mutations in the RAS-MAPK (57%) and PI3K (21%) signaling pathways



- associated loss of *CDKN2A* tumor suppressor gene is also recurrent
  - coexists with mutations in *MAPK* and *PI3K* pathway genes



BRAF V600E not detected in this study, but has been reported in other studies

Go H et al. *Histopathology*. 2014 Aug;65(2):261-72.
Shanmugam V. et al. *Mod Pathol*. 2019;32:830–843.
Hornick JL et al. *Am J Surg Pathol*. 2004;28(9):1133-1144.

Slide courtesy of Dr. V. Shanmugam

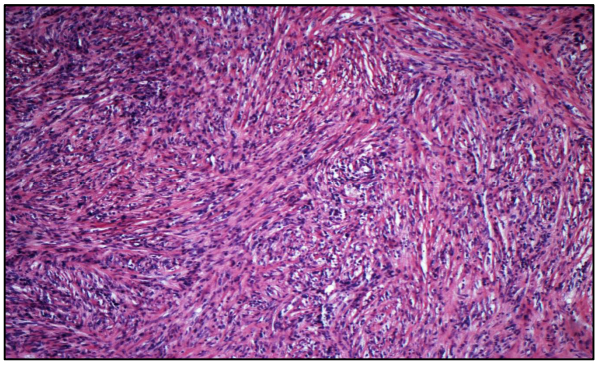
INTERDIGITATING DENDRITIC CELL SARCOMA

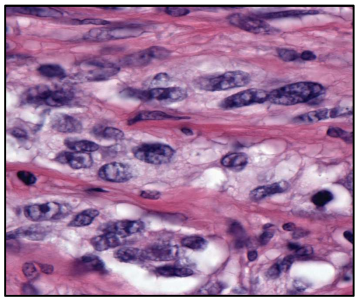
Clinical features & morphology

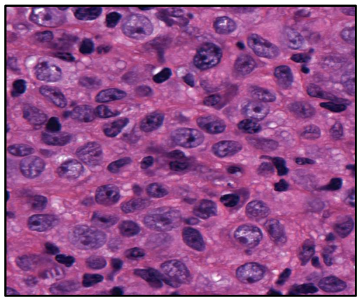
- interdigitating dendritic cell: antigen-processing cells in T-cell rich zones

- rare
- commonly presents as asymptomatic mass
- LN > extranodal sites
- prognosis varies; 2-year OS for localized (68.5%) vs. systemic (15.8%) disease
- may be past history of hematologic or solid tumor malignancy

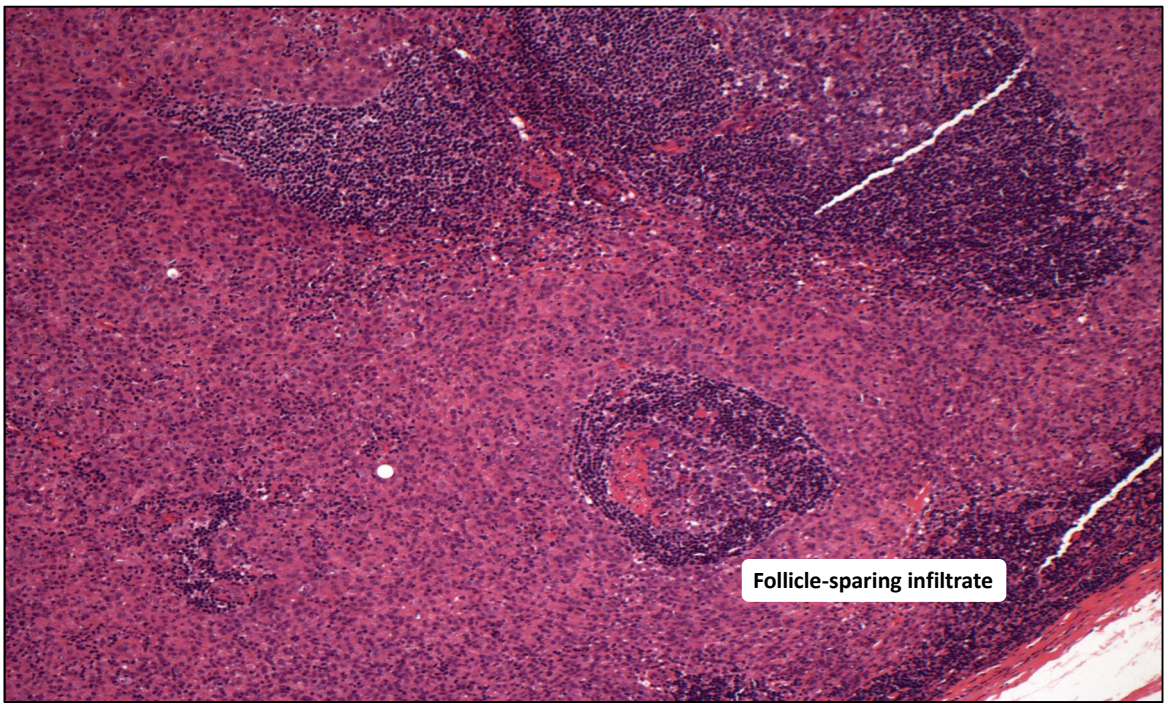
- storiform architecture
- classically spares follicles
- spindled and ovoid cells
- vesicular chromatin, indistinct cell borders, eosinophilic cytoplasm
- admixed small lymphocytes
- low mitotic rate
- typically frank necrosis is not seen







Ninkovic S et al. *Pathology*. 2017 Oct;49(6):643-646.



INTERDIGITATING DENDRITIC CELL SARCOMA

Immunophenotype

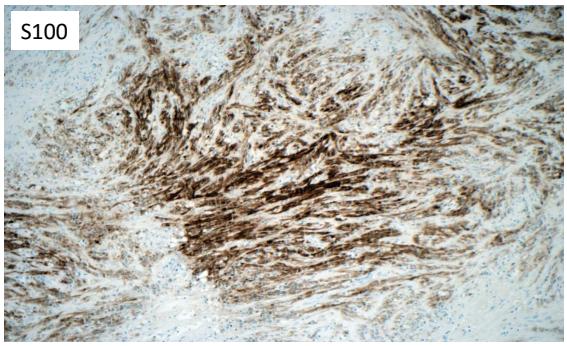
- CD45RO+
- S100+
- CD45+/-
- CD68+/-, lysozyme+/-
- PU.1+ in our lab
- negative for CD21, CD23, CD35 (+ in follicular dendritic cell sarcoma, which is a morphologic mimic)
- *negative for CD1a and langerin*
- *BRAF V600E* mutations have been described

Spindle Cell Melanoma and Interdigitating Dendritic Cell Sarcoma

Do They Represent the Same Process?

Anne M. Stowman, MD, Stacey E. Mills, MD, and Mark R. Wick, MD

Am J Surg Pathol • Volume 40, Number 9, September 2016



IDCS Patient	SOX-10	MiTF
1	Strong nuclear	Negative
2	Strong nuclear	Negative
3	Strong nuclear	Negative
4	Strong nuclear	Negative
5	Strong nuclear	Negative
6	Strong nuclear	Negative
7	Strong nuclear	Negative
8	Strong nuclear	Negative

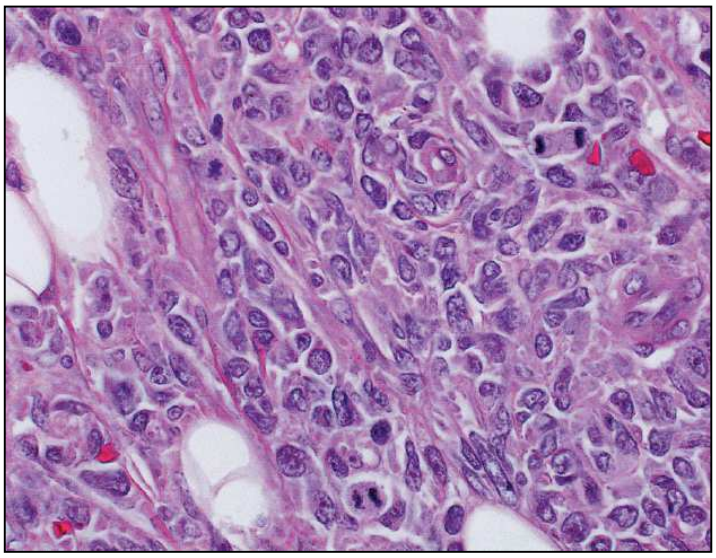
SOX10 - SOX family of transcription factors; neural crest and peripheral nervous system development; melanoma, MPNST

IDCS negative for SOX10 in our lab – extreme caution needed before rendering dx of IDCS if SOX10+, despite reports in literature. Perform full melanoma work-up if SOX10+!

Fachetti F et al. *Virchows Arch* 2017;471:467–489.

LANGERHANS CELL SARCOMA

- extremely rare
- same immunophenotype as LCH (S100+, CD1a+, langerin+) but very high Ki67
- does not arise from LCH
- distinguished from LCH by:
  - *morphology* - marked nuclear pleomorphism, numerous mitoses (>50 per 10 high-powered fields)
  - *clinical course* - aggressive, rapid
- cells may show "grooves" as in LCH
- eosinophil infiltrate not a consistent feature
- single or multiple anatomic sites
  - typically extranodal (skin, bone, soft tissue)
- *BRAF V600E* mutation has been described



Ferringer T et al. *Am J Dermatopathol.* 2006. 28:36–39.

AT A GLANCE

	Progenitor	Key IHC	5th ed. WHO Histiocytic/Dendritic Cell Neoplasms Chapter (preliminary)				Histiocyte Society Classification
Langerhans cell histiocytosis	Hematopoietic	S100, CD1a, Langerin	Yes				L group
Indeterminate dendritic cell tumor	Hematopoietic	S100, CD1a		Yes			L group
Erdheim-Chester disease	Hematopoietic	"Macrophage" markers			Yes		L group
Juvenile xanthogranuloma	Hematopoietic	"Macrophage" markers			Yes (modified heading)		L group/C group
ALK-related histiocytosis	Hematopoietic	"Macrophage" markers; ALK1			Yes (new)		L group
Rosai-Dorfman disease	Hematopoietic	"Macrophage" markers; S100			Yes (new)		R group/C group
Histiocytic sarcoma	Hematopoietic	"Macrophage" markers			Yes		M group
Interdigitating dendritic cell sarcoma	Hematopoietic	S100; variable CD68, lysozyme		Yes			M group
Langerhans cell sarcoma	Hematopoietic	S100, CD1a, Langerin	Yes				M group
Blastic plasmacytoid dendritic cell neoplasm	Hematopoietic	Gabe Griffin will discuss				Yes (new)	N/A
Follicular dendritic cell sarcoma *Inflammatory EBV+ FDCS*	Mesenchymal	CD21, CD23, CD35 *EBV*	No (different chapter)				N/A
Fibroblastic reticular cell tumor	Mesenchymal	SMA, desmin, cytokeratin (dendritic pattern), CD68	No (different chapter)				N/A

TAKE-AWAYS

- variable classification systems
  - WHO (current 4th revised edition; some modifications in forthcoming 5th edition)
  - Histiocyte Society
- S100+
  - Langerhans cell histiocytosis, Langerhans cell sarcoma, indeterminate dendritic cell tumor, interdigitating dendritic cell sarcoma, Rosai-Dorfman disease, -/+ histiocytic sarcoma, -/+ Erdheim-Chester, +/- ALK-related histiocytosis
  - melanoma is much more common than these diagnoses – always consider it (esp. spindle-cell melanoma) in your work-up
- $BRAF^{V600E}$ and ALK1 IHC and genetic analysis (particularly for RAS-MAPK or PI3K signaling pathway alternations) recommended
  - may provide evidence of clonality in cases with morphologic overlap with reactive conditions
    - cyclin D1 and pERK IHC expression can imply activation of the RAS-MAPK signaling pathway
  - may reveal therapeutic targets
- histiocytic and dendritic cell neoplasms may arise following immature or mature hematopoietic neoplasms
  - consider them in the differential diagnosis of spindled or large-cell neoplasms arising in this setting

IMMUNOHISTOCHEMISTRY (APPENDIX)

Antigen	Main reactivity in normal cells	Diagnostic usefulness, pearls, and pitfalls
BRAF V600E	None	High sensitivity and specificity for cells carrying this mutation (clone VE1). The mutation itself is not specific for any disease and may occur also in epithelial cancers and melanoma
CD1a	LC, dermal DC (subset), IDC (subset)	Required for diagnosis of LCH/LCS and IND-DCT Positivity excludes IDCS
CD4	All DC and H/M	Limited usefulness, due to wide expression Generally diffuse cytoplasmic stain, in contrast to T cells where it is membranous
CD14	H/M	H/M-derived tumors (less frequently than in monocytic leukemias)
CD68	H/M PDC	Most H/M-derived tumors show diffuse granular cytoplasmic reactivity; positivity in DC neoplasms more variable; BPDCN often negative Clone PGM1 should be preferred to others since it does not stain myeloid cells
CD123	PDC and activated H/M	High sensitivity and specificity for BPDCN Can be expressed in LCH and in H/M-derived tumors
CD163	H/M	High sensitivity and specificity for H/M-derived tumors
CD207/langerin	LC, IDC (subset)	Defining LCH/LCS. Excludes IDCS
CD303/BDCA2	PDC	High specificity for BPDCN
Factor XIIIa	H/M	H/M-derived tumors
HLA-DR	H/M, DC	Paranuclear dot expression in LCH/LCS, IND-DCT, and IDCS. Useful to distinguish tumoral from reactive LC proliferations (see text)
Lysozyme	H/M	H/M-derived tumors
S100 protein	LC, IDC, activated H/M	Required for diagnosis of LCH/LCS, IND-DCT, IDCS Tumoral H/M can express S100 in variable number of cells Required for diagnosis of RDD
TCL1	PDC	High sensitivity and specificity for BPDCN

LC Langerhans cells, *DC* dendritic cells, *IDC* interdigitating dendritic cells, *LCH* Langerhans cell histiocytosis, *LCS* Langerhans cell sarcoma, *IND-DCT* indeterminate dendritic cell tumor, *IDCS* interdigitating dendritic cell sarcoma, *H/M* histiocytes/macrophages, *PDC* plasmacytoid dendritic cells, *BPDCN* blastic PDC neoplasm, *RDD* Rosai-Dorfman disease

Macrophage Markers	Also reactivity in…
CD68: glycoprotein present in lysosome, phagosomes, and neutrophil primary granules (cytoplasmic; may be granular)	*Depends on clone (PG-M1 more specific than KP-1)* Myeloid cells Mast cells Lymphocytes Some epithelial cells/tumors Schwannoma Granular cell tumor Melanoma (subset)
CD163: plasma membrane glycoprotein (membranous/cytoplasmic)	AML with monocytic differentiation Giant cell tenosynovial tumor Littoral cell angioma
Lysozyme: glycoside hydrolase (cytoplasmic; may be granular)	Granulocytes/myeloid malignancies Some epithelial cells/epithelial neoplasms Granuloma annulare
PU.1: transcription factor (nuclear)	Granulocytes B-lineage

Fachetti F et al. *Virchows Arch* 2017;471:467–489.

IMMUNOHISTOCHEMISTRY (APPENDIX)

Disease	ECD	JXG/AXG	ALK⁺ histiocytosis	RDD	LCH
Immunophenotype					
CD68 (cytoplasmic)	++	++	++	++	+ (paranuclear cytoplasmic dot)
CD163 (surface)	++	++	++	++	—
CD14 (surface)	++	++	++	++	—
CD1a (surface)	−	−	−	−	++
CD207 (Langerin) (cytoplasmic)	−	−	−	−	++
S100 (cytoplasmic/ nuclear)	−/+ (light)	−/+ (light)	−/++ (in some cases dark staining)	+	+
Factor XIIIa (cytoplasmic)	+	+	+	+	−
Fascin (cytoplasmic)	+	+	+	+	−
CD45 (light surface)	+	+	+	+	+
BRAF VE1 (cytoplasmic)	++*	− (Positive cases should be strongly favored to be in ECD family)	−	− (Rare case reports ++)	++*
ALK (cytoplasmic)	++*	++*	++*	−	−
NTRK1(cytoplasmic)	++*	++*	−	−	−

Goyal G et al. *Blood*. 2020; 135(22):1929-45.