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Histiocytic and Dendritic tumors (and something else)
Presentations and Digital Slide Seminar

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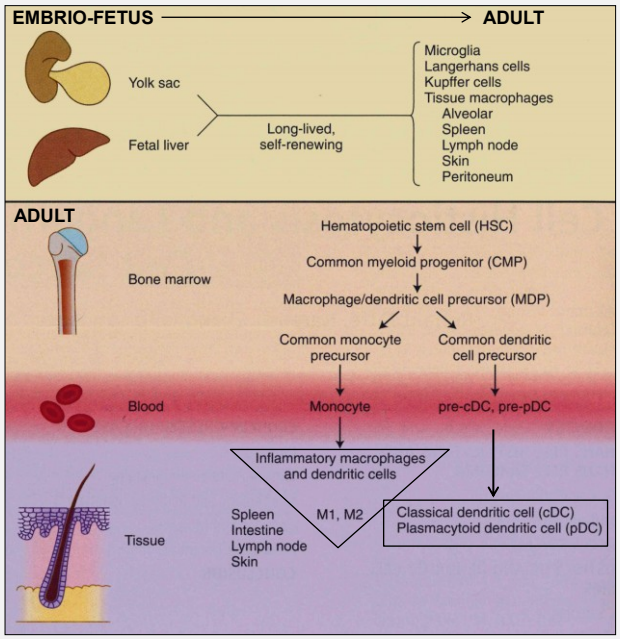
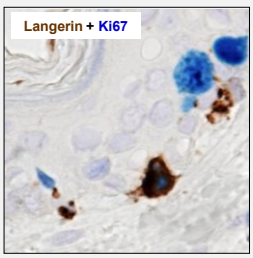
Dipartimento di Medicina Molecolare e Traslazionale
Università degli Studi di Brescia

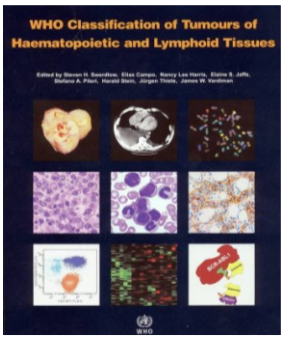
forPath

Brussels, Saturday 28 april 2018





2%-3% of LCs are mitotically active (self-maintainance)



2008

HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	
Histiocytic sarcoma	9755/3
Langerhans cell histiocytosis	9751/3
Langerhans cell sarcoma	9756/3
Interdigitating dendritic cell sarcoma	9757/3
Follicular dendritic cell sarcoma	9758/3
Fibroblastic reticular cell tumour	9759/3
Indeterminate dendritic cell tumour	9757/3
Disseminated juvenile xanthogranuloma	

2017

Histiocytic and dendritic cell neoplasms	
Histiocytic sarcoma	9755/3
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NEW Disseminated juvenile xanthogranuloma	XXXX/X
Erdheim–Chester disease	9750/1

Mesenchymal (non-haematopoietic) origin

9727/3 Blastic plasmacytoid dendritic cell neoplasm

(Myeloid neoplasm)

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

Jean-François Emile[1,2], Oussama Abla[3], Sylvie Fraitag[4], Annacarin Horne[5], Julien Haroche[6,7], Jean Donadieu[8,1], Luis Requena-Caballero[9], Michael B Jordan[10], Omar Abdel-Wahab[11], Carl E Allen[12], Frédéric Charlotte[13,7], Eli L Diamond[14], R Maarten Egeler[3], Alain Fischer[15-16], Juana Gil Herrera[17], Jan-Inge Henter[18], Filip Janku[19], Miriam Merad[20], Jennifer Picarsic[21], Carlos Rodriguez-Galindo[22], Barret J Rollins[23], Abdellatif Tazi[24], Robert Vassallo[25] and Lawrence M Weiss[26] for the Histiocyte Society

Blood. 2016 Mar 10. pii: blood-2016-01-690636. [Epub ahead of print]

Histiocytoses of the L group
- **Langerhans cell histiocytosis (LCH)**
- **Indeterminate cell histiocytosis (ICH)**
- **Erdheim-Chester disease Classical type**
- **Extra-cutaneous or disseminated JXG with MAPK activating mutation or ALK translocations**
- **Mixed ECD & LCH**

Non-Langerhans Cell Histiocytoses of skin and mucosa (C group)
- **Cutaneous non-LCH histiocytoses**
  - **Xanthogranuloma (XG) family**
  - **Non XG family**
- **Cutaneous non-LCH histiocytoses with a major systemic component**

Malignant histiocytoses (M group)
- **Histiocytic**
- **Interdigitating cell**
- **Langerhans cell**
- **Indeterminate cell**
- **Not specified**

Rosai-Dorfman Histiocytoses (R group)

Haemophagocytic Lymphohistiocytosis (H group)

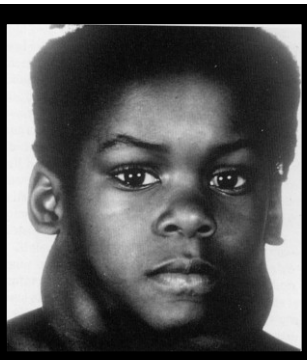
Reactive processes (? RDD)
Significant morbidity

ROSAI-DORFMAN DISEASE
(Sinus Histiocytosis with Massive Lymphadenopathy)

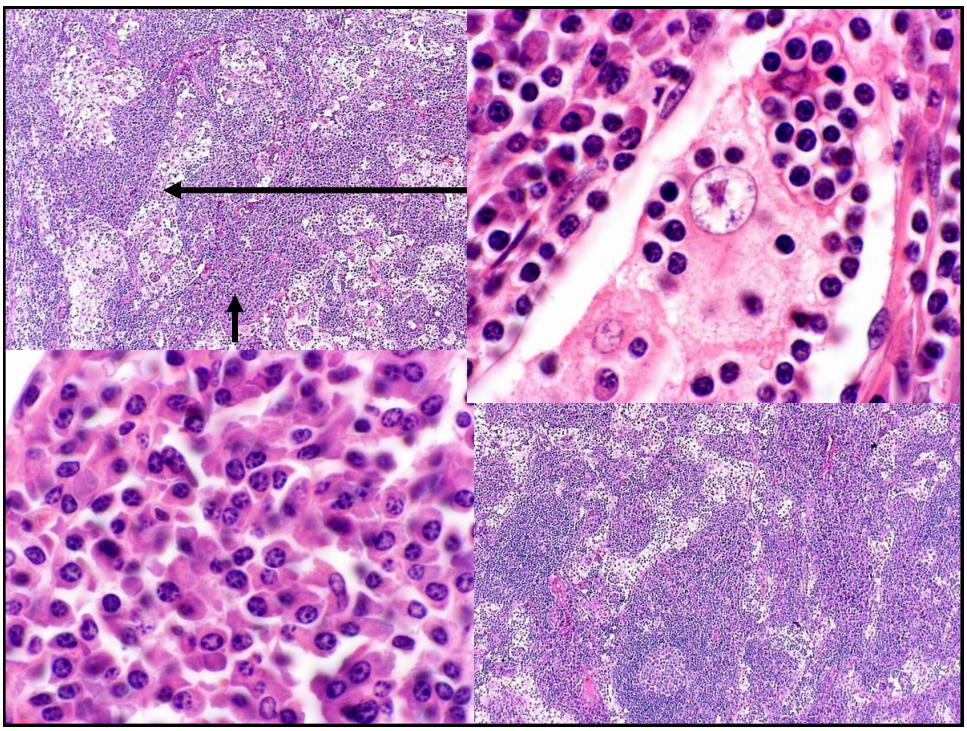
- Histiocytic proliferation expressing S100 and various macrophage markers, but negative for CD1a and Langerin

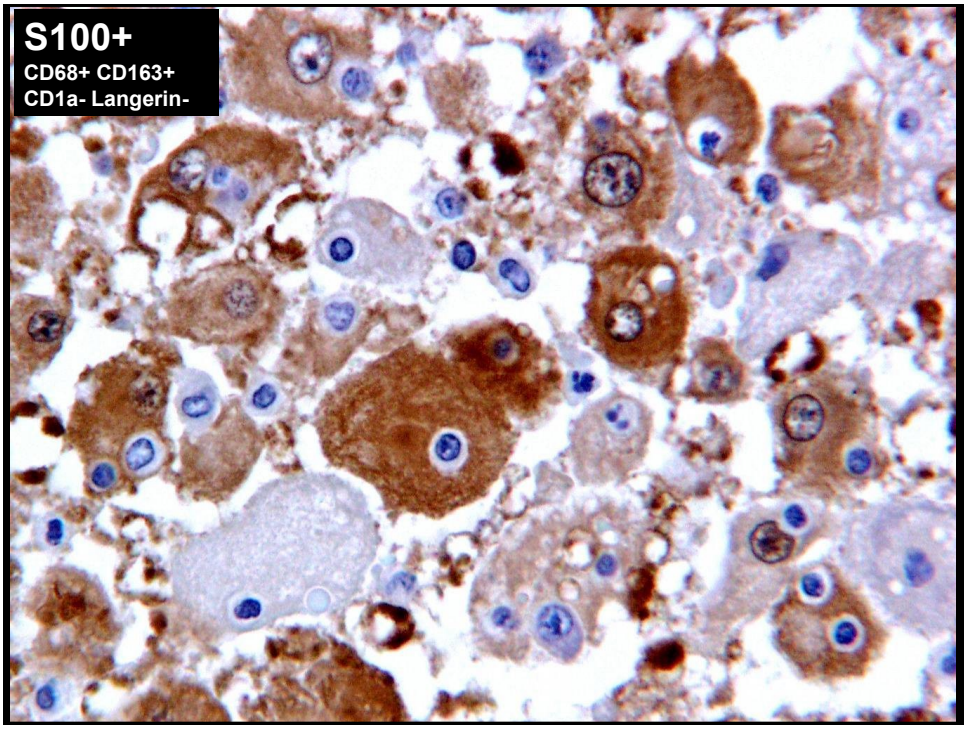
Classical presentation
- Young adults (>80%)
- Fever, weight loss, night sweats, fatigue, angina
- ESR increase, polyclonal gammopathy, anemia
- Mostly adenopathy (> cervical)
- Extranodal (43%): skin, nasal cavity, bone, retro-orbital tissue

- Benign (self-limiting; regression), but 5%-11% may die due to vital organs involvement



Soonchunhyang Med Sci 2014





ROSAI-DORFMAN DISEASE
(Sinus Histiocytosis with Massive Lymphadenopathy)

Inherited conditions predisposing to RDD or RDD-like lesions

H syndrome (Faisalabad histiocytosis/Familial RDD)

- Autosomal recessive genodermatosis mutation of *SLC29A3* gene
- Hyperpigmentation, Hypertrichosis, Hepatosplenomegaly, Hearing loss, Heart anomalies, Hypogonadism, low Height (short stature), Hyperglycemia, Hallux valgus

- RDD lesions in lymph nodes (20% of patients), skin, nasal

ALPS (Autoimmune Lymphoproliferative Syndrome)

- Type Ia (*TNFRSF6* heterozygous germline mutations encoding Fas)
- More often males, earlier presentation, more severe ALPS

- RDD-like changes in lymph nodes of 41% of Type Ia ALPS patients

ROSAI-DORFMAN DISEASE
(Sinus Histiocytosis with Massive Lymphadenopathy)

KRAS, NRAS, and MAP2K1 mutations reported

- Diamond EL, et al. Cancer discovery 2016
- Shanmugam V, et al. Head and Neck Pathol 2016
- Matter MS, et al. Virchows Archiv 2017
- Garces S, et al. Mod Pathol 2017
- Jacobsen E, et al. NEJM 2017

Garces S, et al. Mod Pathol 2017

Point mutations in 7/21 (33%) cases
- ***KRAS*** **(n = 4)**
- ***MAP2K1*** **(n = 3)**

No mutations in ARAF, BRAF, PIK3CA (and others of 134 NGS analyzed genes)

Mutated RDD :
- **Younger age**
- **Head and neck region**
- **Multifocal presentation**
- **NO relationship to clinical outcome (remission or persistence)**

Histiocytic Sarcoma

Neoplastic proliferation with features of histiocytes. Extramedullary myeloid tumors with monocytic differentiation (e.g. acute monoblastic leukemias) *and dendritic cell neoplasms are excluded* (WHO 2008)

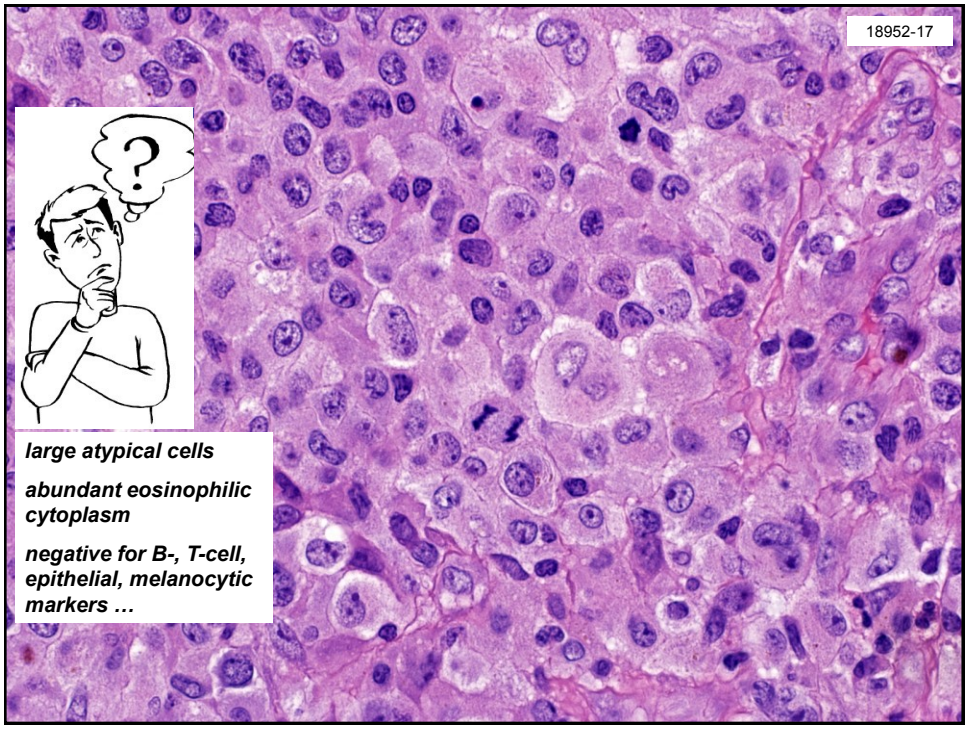
Neoplastic proliferation with features of histiocytes. Extramedullary myeloid tumors with monocytic differentiation (e.g. acute monoblastic leukemias) are excluded (WHO 2017)

- Rare
- Wide age range (median: 52 y)

- Mostly **extranodal** (intestinal tract, skin and soft tissues)
- Solitary mass, with systemic symptoms (fever and weight loss)
- In rare cases: systemic presentation ("***Malignant Histiocytosis***")

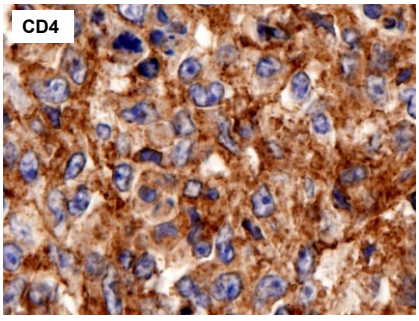
- Most patients (60−80%) die of progressive disease
- Better outcome if localized disease and small primary tumours

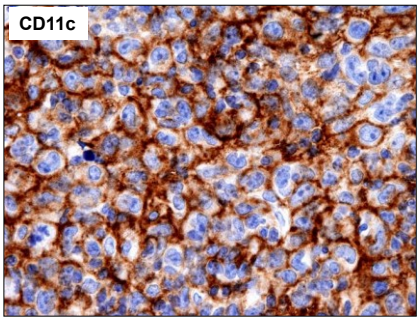
- May be associated with:
  - **Mediastinal non-seminomatous germ cell tumour** (commonly malignant teratoma, ± yolk sac component)
  - **Non-Hodgkin's lymphoma** (usually follicular lymphoma)



Histiocytic Sarcoma

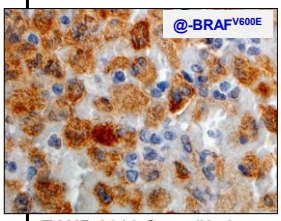
Positive (one or more)	"Must" be negative		Irrelevant
CD4 CD11c, CD14 CD68 CD163 Lysozyme CD45 HLADR	CD1a Langerin B-cell & T-cell specific markers	CD21 CD23 CD30/ALK CD34 MPO	S100 (focal) CD15 (weak)
	CKs MART1, HMB45		



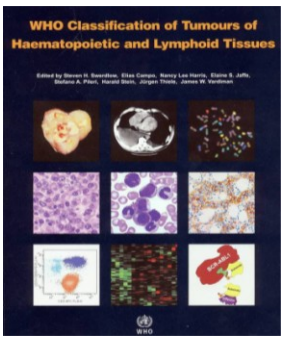


Histiocytic Sarcoma

- **Frequent chromosomal gains and losses**
- **Variable results on the presence of *BRAF*^{V600E} mutations:**
  - **5/8** (*Go H, et al. Histopathology 2014*)
  - **0/8** (*Haroche J, et al. Blood 2012; Liu Q, et al. Virchow Arch 2016*)
- ***Non BRAF*^{V600E} mutations ± others in 5/5 HS** (*Liu Q, 2016*)
  - ***BRAF***^{G464V} (***KRAS*** **Q61H**)
  - ***BRAF***^{G466R}
  - ***BRAF***^{N581S} (***TP53***^{Y263H}, ***PTEN***^{L125E}, ***PTEN***^{R130Q})
  - ***PTPN11***^{G503V}
  - ***PIK3CA***^{H104L}
- **HS arising in mediastinal germ cell tumour show identical isochromosome 12\p**
- **HS associated with B-cell lymphoma may have identical clonal IGH rearrangements**
- **HS associated with t(14;18)-positive follicular lymphoma may have identical chromosomal breakpoints in the *BCL2* locus**
- ***De novo*** **HS may have clonal IGH rearrangements**



EAHP 2016 Case #243



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Erdheim–Chester disease	9750/1

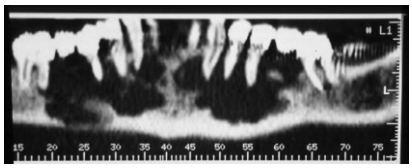
Langerhans Cell Histiocytosis
Langerhans Cell Sarcoma

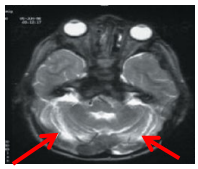
Langerhans cell histiocytosis (LCH) is a clonal neoplastic proliferation of Langerhans-type cells that express CD1a, langerin and S100 protein, and shows Birbeck granules by ultrastructural examination.

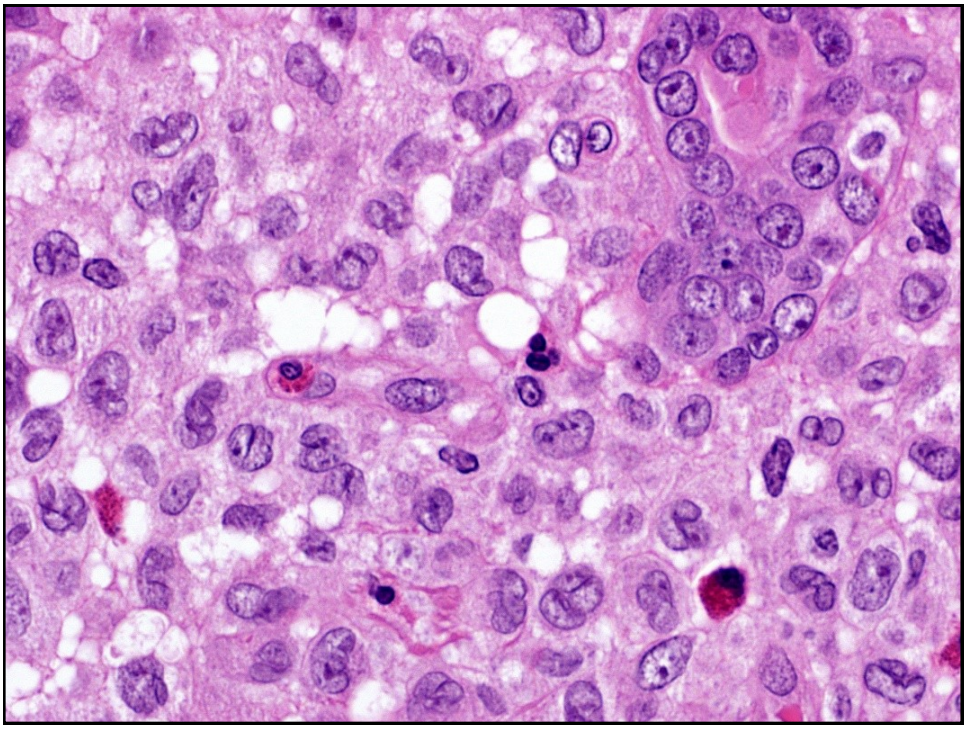
Langerhans cell sarcoma (LCS) is a high-grade neoplasm with overtly malignant cytologic features and the Langerhans cell phenotype.

(WHO 2008, 2017)

- **Hematopoietic origin**
- **Sex: M:F=2:1**
- **Children: 1/25.000 /year**
- **Adult: 1-2 cases/1.000.000 /year**
- **Single or multiorgan disorder**
- **Highly heterogeneous clinical behavior: easily curable, chronic indolent, chronic active, rapidly aggressive**



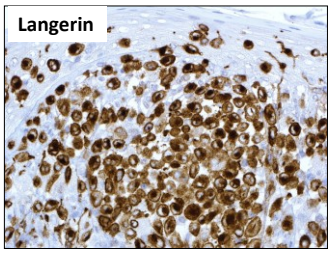


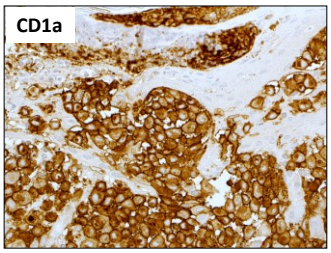


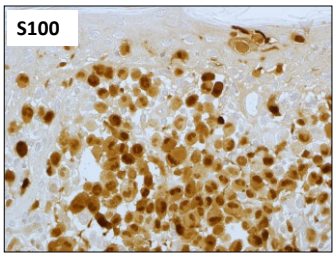
LCH

Diagnostic Markers

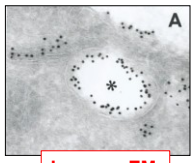
- Langerin/CD207
- CD1a
- S100



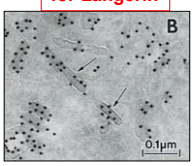




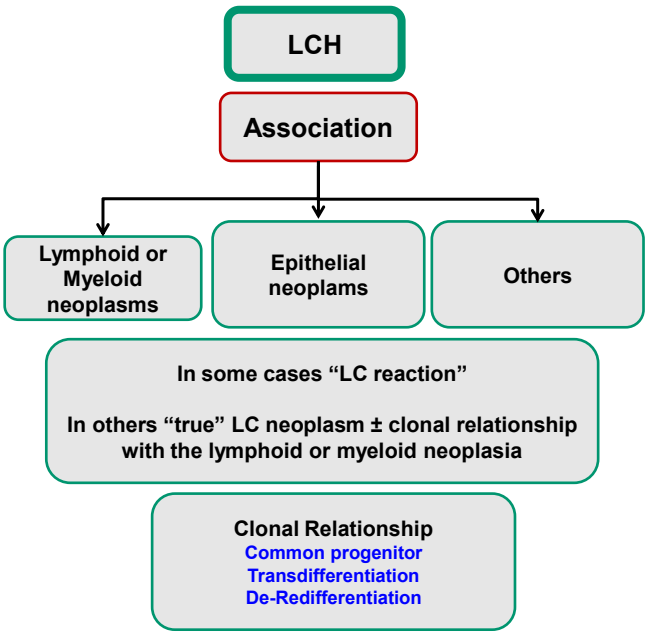
Birbeck granules



Immuno EM for Langerin



Molecular Biology of the Cell 2002: 13: 317



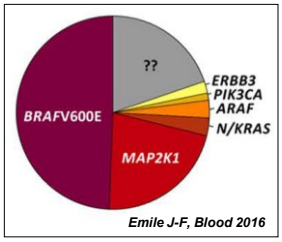
Langerhans Cell Histiocytosis

Critical role of MAPK signaling in LCH
ERK activation is a universal endpoint

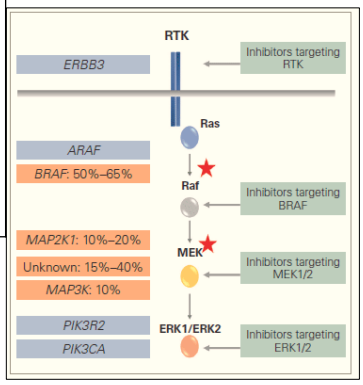
- ***BRAF*** ^{V600E} **mutation (~50%)** in LCH
- 50% of BRAF wild-type cases show mutations of ***MAP2K1***
- Other more rare mutations: ***ARAF, NRAS, PIK3CA, ERBB3***

- **Efficacy** of **vemurafenib** in *BRAF* ^{V600E} mutated **multisystemic and refractory LCH**

•Badalian-Very G (Blood, 2010)
•Haroche J (Blood, 2012)
•Haroche J (Blood, 2013)
•Brown NA (Blood, 2014)
•Chakraborty (Blood, 2014)
•Alayed (Hum Pathol 2016)



Emile J-F, Blood 2016



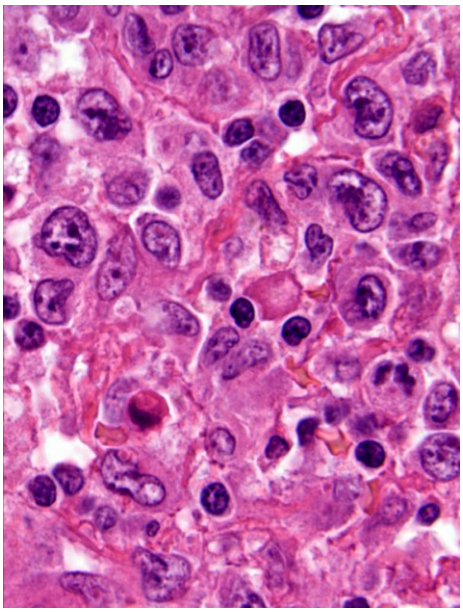
Zinn DJ, 2016

Langerhans Cell Histiocytosis

Badalian-Very G (2010)	***BRAF*** ^{V600E} **mutation (~50%)** in LCH *(Blood, 2010)*
Haroche J (2012)	***BRAF*** ^{V600E} **mutation** in LCH and Erdheim-Chester's disease *(Blood, 2012)* → ***Useful in diagnosis***
Haroche J (2013)	**Efficacy** of **vemurafenib** in *BRAF* ^{V600E} mutated multisystemic and refractory **LCH** and **Erdheim-Chester's disease** *(Blood, 2013)* → ***Useful in treatment (@-BRAF)***
Brown NA (2014) **Chakraborty R (2014)**	• 50% of BRAF wild-type cases show mutations of ***MAP2K1*** *(Blood, 2014; Blood 2014)* • LCH BRAF^{wt} may have mutations of ***ARAF, NRAS, PIK3CA, ERBB3*** (Blood, 2014; 2016) →**Critical** role of **MAPK signaling** in LCH (ERK activation is a universal endpoint in LCH) → ***Potentially useful in treatment***
Héritier S (2016)	***BRAF*** ^{V600E} **mutation** ***correlates with high risk disease and increased resistance to first line treatment***
Berres ML (2014), Kobayashi M (2014), Collen M (2015), Héritier S (2017), Milne P (2017)	***BRAF*** ^{V600E} **mutation** ***detection in precursor cells or in plasma cell-free DNA represents a marker of active and high risk LCH*** → ***Prognostic***

Langerhans Cell Sarcoma

- Very rare, cutaneous and systemic
- Aggressive
- Primary or progression from LCH
- Marked cytological atypia, mitoses
- *LC cytological traits not recognizable*
- Ki67 generally high: 10%-70% (highly variable also in LC Histiocytosis)
- Phenotype: more variable expression of LC markers
- BRAF mutation in rare cases
- Some positive for Merkel PV



Indeterminate dendritic cell tumour

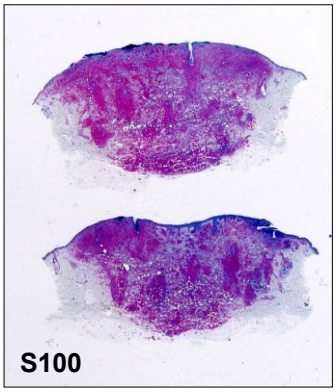
Indeterminate dendritic cell tumour / Indeterminate cell histiocytosis
Neoplastic proliferation of spindled to ovoid cells with phenotypic features similar to those of normal indeterminate cells, the alleged precursor cells of Langerhans cells (never uniquivocally identified)

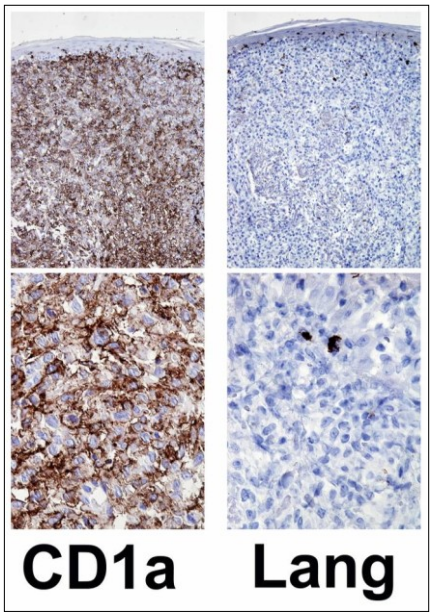
(WHO, 2008, 2017).

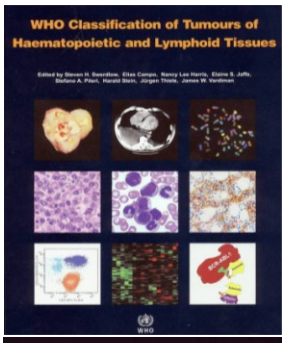
- Rare
- Skin (single, multiple)
- Systemic symptoms usually absent
- Usually indolent; exceptionally visceral involvement and fatal evolution
- Some associated with low-grade B-cell lymphoma.
- Morphology very similar to LCH; cases with atypical features reported
- S100^{+} CD1a^{+} Langerin^{-}
- *ETV3-NCOA2* translocation (3 cases; Brown, Blood 2015)
- BRAF^{V600E} (1 case)

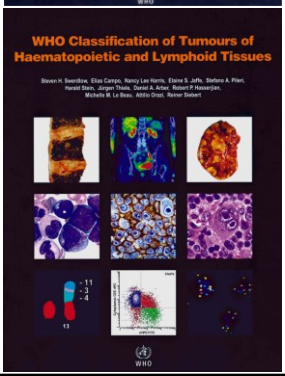
Courtesy Dr. Cristina Mitteldorf

Indeterminate dendritic cell tumour









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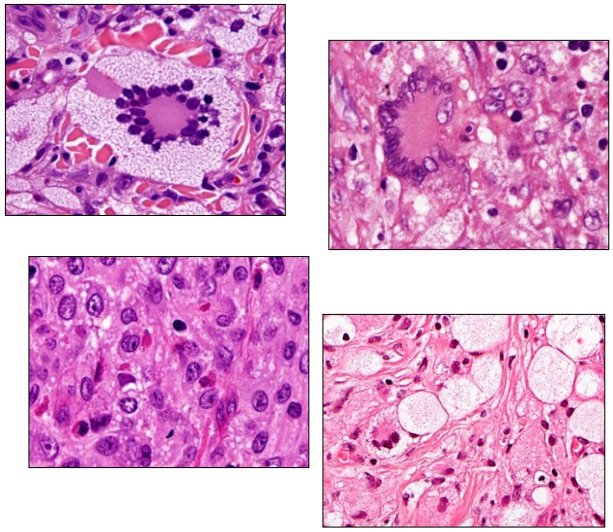
Xanthogranuloma (normolipidemic) spectrum

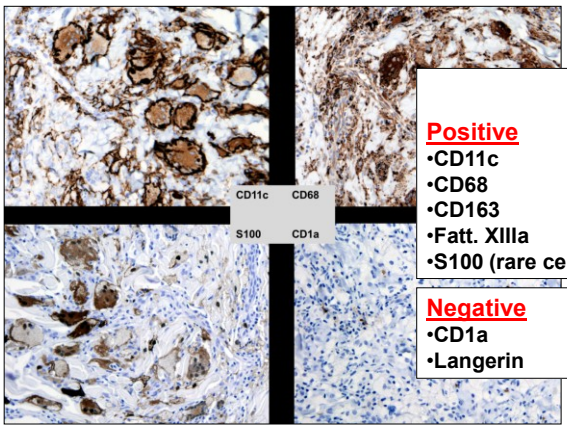
- Juvenile XG
- Disseminated XG
- Erdheim Chester Disease



Morphological and phenotypical overlap

Xanthogranuloma (normolipidemic) spectrum

- Juvenile XG
- Disseminated XG
- Erdheim Chester Disease



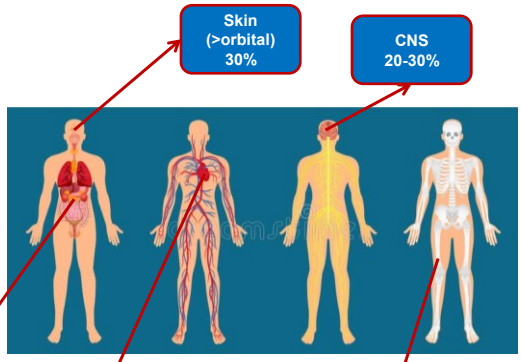
Positive
- CD11c
- CD68
- CD163
- Fatt. XIIIa
- S100 (rare cells)

Negative
- CD1a
- Langerin

Morphological and phenotypical overlap

Erdheim-Chester disease
(Polyostotic Sclerosing Histiocytosis)

- Rare, but recognition increased drastically over the past decade
- Mean age at diagnosis: 55-60 years
- Rare pediatric cases (< 15 reported)
- Clonal systemic proliferation of macrophages, commonly with a foamy (xanthomatous) component and multinucleated (Touton) giant cells
- Diagnosis based on clinical, imaging, and histological features
- Sometimes associated with LCH ("mixed histiocytosis")



Erdheim-Chester disease
(Polyostotic Sclerosing Histiocytosis)

CLINICAL PRESENTATION AND SYMPTOMS EXTREMELY VARIABLE

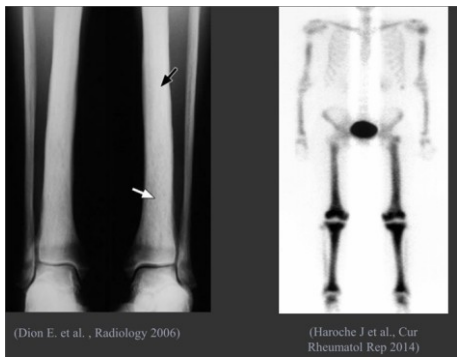
- Bone pain (30%) at any time during the course of the disease
- SKIN. First manifestation in 20% of cases.
  Xanthelasma of eyelids or periorbital tissue
  Other lesions possible (papules/nodules, erythematous plaques)
- Orbital infiltration, often bilateral → exophthalmos, pain, oculomotor nerve palsies, or blindness.
- Cardiovascular involvement may be asymptomatic and detected incidentally by MRI or CT
  Clinical consequences usually not severe, except for renovascular hypertension (small number of cases)
- Pericardium involvement: pericarditis, effusion, or even tamponade.
- Pituitary gland infiltration → diabetes insipidus and others
- CNS involvement :variable symptoms
- The most serious neurological complication: neurodegenerative cerebellar disease (15-20% of patients)

Courtesy Dr. E Berti

Erdheim-Chester disease
(Polyostotic Sclerosing Histiocytosis)

Imaging

- **Bones**
  - **X-ray**: bilateral and symmetric cortical osteosclerosis (diaphysis and metaphysis of the long bones
  - **99Tc bone scintigraphy:** symmetric and abnormally intense labeling
  - **PET** high specific for the diagnosis of bone involvement

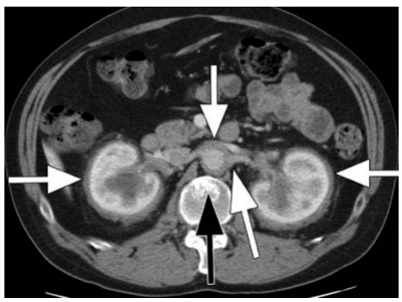


- Lytic and sclerotic lesion distal femur and proximal tibia
- Destruction of the anterior femoral cortex, impacted pathological fracture through the lesion
- Anterolateral soft tissue mass extending from the destroyed femur (arrow)

Erdheim-Chester disease
(Polyostotic Sclerosing Histiocytosis)

Imaging

- **Cardiovascular**
  - Circumferential sheathing of the thoracic or abdominal aorta ("**coated aorta**") and large arteries
- **Retroperitoneal**
  - Prominent renal capsule/ureters involvement: → "**hairy kidney**"



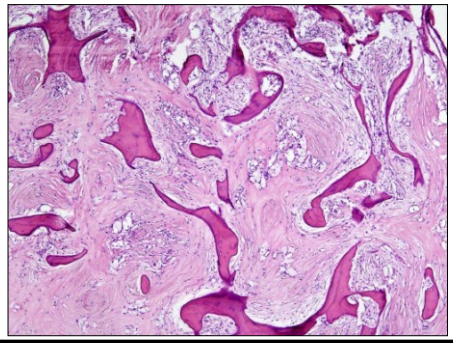
N Engl J Med 359: 736-47

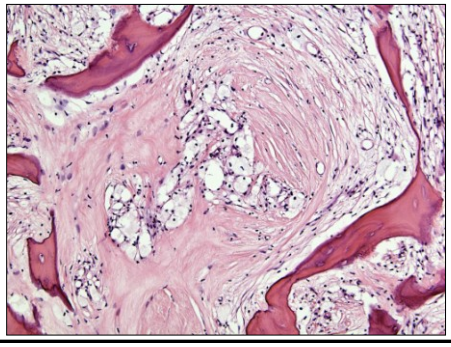
Erdheim-Chester disease
(Polyostotic Sclerosing Histiocytosis)

- Histiocytes, often foamy
- Touton-cells
- Other inflammatory cells variable
- Fibrosis, can be prominent and obscures the histiocytes

Easily misdiagnosed as a reactive process

- Macrophage phenotype
- S100 can be expressed
- CD1a and Langerin negative

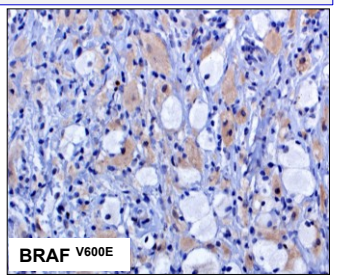




Erdheim-Chester disease
(Polyostotic Sclerosing Histiocytosis)

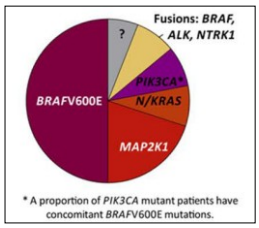
Genetic profile
- Clonal (classical cytogenetics, other techniques)
- Activating mutations in MAPK pathway genes (*):
  - *BRAF* V600E (~50%)
  - *MAP2K1, NRAS, KRAS point mutations*
- *ALK* translocations
- Recurrent mutations in the PI3K pathway gene *PIK3CA*

(*) all ECD have at least one mutation activating the MAP-kinase pathway (Cancer Discov 2016; 6:154-65)



Prognosis and predictive factors
- Chronic disease (indolent → aggressive)
- Outcome correlates with sites and extension of involvement (worse in CNS or multisystemic disease)

Overall survival
- 43% of patients alive after average follow-up of 32 months (old series)
- OS improved with interferon-alpha therapy (68% at 5 years)
- Verumafenib (@-BRAF) and Cobimetinib (@MEK) recently used with promising results



Emile J-F, Blood 2016