Histiocytic and Dendritic tumors (and something else)

Presentations and Digital Slide Seminar

Fabio Facchetti
Dipartimento di Medicina Molecolare e Traslazionale
Università degli Studi di Brescia

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2%-3% of LCs are mitotically active (self-maintainance)
### Histioctyes 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 Histioctyes 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 histioctyes (M group)
- Histiocytic
- Interdigitating cell
- Langerhans cell
- Indeterminate cell
- Not specified

### Rosai-Dorfman Histiocytoses (R group)

### Haemophagocytic Lymphohistiocytosis (H group)

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**Revised classification of histioctyes and neoplasms of the macrophage-dendritic cell lineages**

Jean-François Emile1,2, Oussama Abla3, Sylvie Fratag4, Annacarin Horne5, Julien Haroche5,6, Jean Donadieu4,1, Luis Requena-Caballero5, Michael B Jordan3, Omar Abdel-Wahab1, Carl E Allen7, Frédéric Charlotte8, Eli L Diamond12, R Maarten Egede1, Alain Fischer13,16, Juana Gil Herrera17, Jan-Ingel Henter18, Filip Janku19, Miriam Meraa20, Jennifer Picarsie21, Carlos Rodriguez-Galindo22, Barret J Rollins23, Abdellatif Tazi24, Robert Vassallo25 and Lawrence M Weiss26 for the Histiocty Society

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

Soon Chun Hyang 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

- Garces S, et al. Mod Pathol 2017
- Jacobsen E, et al. NEJM 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)

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**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)
large atypical cells
abundant eosinophilic cytoplasm
negative for B-, T-cell, epithelial, melanocytic markers ...

**Histiocytic Sarcoma**

<table>
<thead>
<tr>
<th>Positive (one or more)</th>
<th>“Must” be negative</th>
<th>Irrelevant</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 CD11c, CD14 CD68 CD163 Lysozyme CD45 HLADR</td>
<td>CD1a Langerin B-cell &amp; T-cell specific markers</td>
<td>S100 (focal) CD15 (weak) CD21 CD23 CD30/ALK CD34 MPO CKs MART1, HMB45</td>
</tr>
</tbody>
</table>
Frequent chromosomal gains and losses

Variable results on the presence of **BRAF** V600E mutations:

**Non BRAF** V600E mutations ± others in 5/5 HS (Liu Q, 2016)
- **BRAF** G464V (KRAS Q61H)
- **BRAF** G466R
- **BRAF** NS81S (TP53 Y263H, PTEN L125E, PTEN R130Q)
- PTPN11 G503V
- PIK3CA H104L

HS arising in mediastinal germ cell tumour show identical isochromosome 12p

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
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


Lymphoid or Myeloid neoplasms
Epithelial neoplasms
Others

In some cases “LC reaction”
In others “true” LC neoplasm ± clonal relationship with the lymphoid or myeloid neoplasia

Clonal Relationship
- Common progenitor
- Transdifferentiation
- De-Redifferentiation
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)

Langerhans Cell Histiocytosis

<table>
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<tr>
<th>Author(s)</th>
<th>BRAF V600E mutation (~50%) in LCH (Blood, 2010)</th>
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<td>Haroche J (2013)</td>
<td></td>
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<tr>
<td>Brown NA (2014) &amp; Chakraborty R (2014)</td>
<td>50% of BRAF wild-type cases show mutations of MAP2K1 (Blood, 2014; Blood 2014) → Critical role of MAPK signaling in LCH (ERK activation is a universal endpoint in LCH) → Potentially useful in treatment</td>
</tr>
<tr>
<td>Héritier S (2016)</td>
<td>BRAF V600E mutation correlates with high risk disease and increased resistance to first line treatment</td>
</tr>
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</table>
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 unequivocally identified)


- 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)
- BRAFV600E (1 case)
Indeterminate dendritic cell tumour

S100

CD1a  Lang

Histiocytic and dendritic cell neoplasms

Histioctytic 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

Histioctytic sarcoma  9755/3
Tumours derived from Langerhans cells
Langerhans cell histiocytosis  9751/3
Langerhans cell sarcoma  9756/3
Indeterminate dendritic cell tumour  9757/3
Interdigitating dendritic cell sarcoma  9757/3
Follicular dendritic cell sarcoma  9758/3
Inflammatory pseudotumour-like follicular/ fibroblastic dendritic cell sarcoma
Fibroblastic reticular cell tumour  9759/3
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease  9750/1
Xanthogranuloma (normolipidemic) spectrum

- Juvenile XG
- Disseminated XG
- Erdheim Chester Disease

Morphological and phenotypical overlap

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

Negative
- CD1a
- Langerin
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")

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 \(\rightarrow\) 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 \(\rightarrow\) diabetes insipidus and others
- CNS involvement: variable symptoms The most serious neurological complication: neurodegenerative cerebellar disease (15-20% of patients)
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"

Erdheim-Chester disease
(Polyostotic Sclerosing Histiocytosis)

- Histiocytes, often foamy
- Touton-cells
- Other inflammatory cells variable
- Fibrosis, can be prominent and obscures the histiocytes
- Macrophage phenotype
- S100 can be expressed
- CD1a and Langerin negative

Easily misdiagnosed as a reactive process

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 \(\rightarrow\) 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