WHO has an update on the Histiocytoses?...Check your Blood: A brief update on the pathogenesis and histopathology of histiocytic neoplasms

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Society for Hematopathology
Companion Meeting USCAP 2017
Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

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**A Group**
- LCH
- ICH
- ECD
- Mixed LCH/ECD

**C Group**
- Cutaneous non-LCH
  - XG family: JXG, AXG, SRH, BCH, GEH, PNH
  - Non-XG family: cutaneous RDD, NXG, other NOS
- Cutaneous non-LCH with a major systemic component

**R Group**
- Familial Rosai-Dorfman Disease (RDD)
- Sporadic RDD
  - Classical RDD
  - Extra-nodal RDD
  - RDD with neoplasia or immune disease
  - Unclassified

**M Group**
- Primary Malignant Histiocytoses
- Secondary Malignant Histiocytoses (following or associated with another hematologic neoplasia)
  - Subtypes: Histiocytic, Interdigitating, Langerhans, Indeterminate Cell

**H Group**
- Primary HLH: Monogenic inherited conditions leading to HLH
- Secondary HLH (non-Mendelian HLH)
- HLH of unknown/uncertain origin

* A proportion of PIK3CA mutant patients have concomitant BRAF600E mutations.

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

**A**

<table>
<thead>
<tr>
<th>L Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCH</td>
</tr>
<tr>
<td>ICH</td>
</tr>
<tr>
<td>ECD</td>
</tr>
<tr>
<td>Mixed LCH/ECD</td>
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</tbody>
</table>

**Image courtesy of:** Benjamin H. Durham, M.D.,
Genomic Pathology Research Fellow in Molecular Oncology
Department of Pathology Memorial Sloan Kettering Cancer Center

**Langerhans cell histiocytosis (LCH)**

- **BRAF V600E**
- **MAP2K1**
- **Fusions: BRAF, ETV3-NCOA2, ERBB3, ARAF, BRAF Other, K/NRAS**
- **BRAF Indels**

**Erdheim-Chester Disease (ECD)**

- **MAP2K1**
- **K/NRAS**
- **Fusions: ALK, NTRK1, MAP3K1 Amplification, ARAF, PIK3CA**

**References**

- Lee et al. *JCI Insight* 2017
- Go, et al. *Histopathology* 2014
- Kordes, et al. *Leukemia* 2015
- Lee, et al. *JCI Insight* 2017
**Table 1. Histiocytoses of the L group**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Subtypes</th>
</tr>
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<tbody>
<tr>
<td>LCH</td>
<td>LCH SS</td>
</tr>
<tr>
<td></td>
<td>LCH lung^+</td>
</tr>
<tr>
<td></td>
<td>LCH MS-RO^+</td>
</tr>
<tr>
<td></td>
<td>LCH MS-RO^-</td>
</tr>
<tr>
<td></td>
<td>Associated with another myeloproliferative/</td>
</tr>
<tr>
<td></td>
<td>myelodysplastic disorder</td>
</tr>
<tr>
<td>ICH</td>
<td>ECD classical type</td>
</tr>
<tr>
<td></td>
<td>ECD without bone involvement</td>
</tr>
<tr>
<td></td>
<td>Associated with another myeloproliferative/</td>
</tr>
<tr>
<td></td>
<td>myelodysplastic disorder</td>
</tr>
<tr>
<td></td>
<td>Extracutaneous or disseminated JXG with MAPK-</td>
</tr>
<tr>
<td></td>
<td>activating mutation or ALK translocations</td>
</tr>
</tbody>
</table>

**Mixed ECD and LCH**

ECD, Erdheim-Chester disease; ICH, indeterminate cell histiocytosis; LCH, Langerhans cell histiocytosis; MS, multiple system; RO, risk organ; SS, single system.
Original skin biopsy of LCH, later shown to also be VE1+


38 yo F with both skin LCH and ECD
38 yo F with both skin LCH and ECD

2nd skin lesions with XG phenotype and BRAF-V600E+ prompted ECD workup

38 yo F with both skin LCH and ECD

3rd bx: Retroperitoneal biopsy

Erdheim Chester Disease (ECD)

- **MIP** - *Foamy CD68 histiocytes ≠ ECD*
  - Clinicoradiographic correlation with xanthogranuloma phenotype is important
  - Molecular as an additional diagnostic aid

- **Updates to proposed classification**
  - *BRAF* and beyond
  - Myeloid inflammatory neoplasia
  - “L” group lesion with XG immunophenotype
    - LCH
    - ECD (Erdheim Chester Disease)
    - Mixed LCH/ECD
    - ICH (indeterminate cell histiocytosis)

*Morphology, Immunophenotype, Pattern of involvement*
**ECD** = Clinical, Radiographic, and Pathologic

<table>
<thead>
<tr>
<th>Organ system involvement</th>
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<tbody>
<tr>
<td>Skin(^{24,95})</td>
<td>Xanthelasma</td>
</tr>
<tr>
<td></td>
<td>Yellow or red-brown plaques</td>
</tr>
<tr>
<td>Heart(^{15})</td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td></td>
<td>Myocardial infiltration, right atrial mass</td>
</tr>
<tr>
<td></td>
<td>Periaortic sheathing (&quot;coated aorta&quot;)</td>
</tr>
<tr>
<td>Lungs(^{43,96})</td>
<td>Interlobular septal thickening, ground-glass or centrilobular opacities on CT</td>
</tr>
<tr>
<td>Retroperitoneum</td>
<td>Perinephric infiltration</td>
</tr>
<tr>
<td>Liver and spleen</td>
<td>Rare</td>
</tr>
<tr>
<td>Bone(^{33})</td>
<td>Femurs and tibia</td>
</tr>
<tr>
<td></td>
<td>Bone pain</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Reported, but uncharacteristic</td>
</tr>
<tr>
<td>CNS(^{48,97,98})</td>
<td>Cerebellar or brain stem lesions</td>
</tr>
<tr>
<td></td>
<td>Dural-based lesions</td>
</tr>
<tr>
<td></td>
<td>Brain parenchymal lesions</td>
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</tbody>
</table>

CD68+
Xanthomatous histiocytes ≠ ECD

Xanthomatous inflammation
Not ECD
CD68 PGM1

Fascin

CD163

Xanthomatous inflammation
Not ECD

Factor 13a
ECD with pericardial and pleural effusions

ECD with brain involvement
**BRAF and beyond ...ECD**

- **BRAF-V600E**: Highly dependent of the method of testing: Highly sensitive PCR methods are recommended in order to detect small allelic fractions (~1% mutant)
- **BRAF-V600E** can co-occur with **ARAF, PIK3CA** mutations
- New targetable kinase gene fusions*
  - **KIF5B-ALK**
  - **LMNA-NTRK1**


Diverse Kinase Alterations in ECD:

- **BRAF V600E**
- **MAP2K1**
- **K/NRAS**
- **PIK3CA**
- **ARAF**
- **MAP3K1 Amplification**
- **Fusions: ALK, NTRK1**
- **Wild Type**

References:
- Kordes, et al. Leukemia 2015
- Lee, et al. JCI Insight 2017

Image courtesy of: Benjamin H. Durham, M.D., Genomic Pathology Research Fellow in Molecular Oncology Department of Pathology Memorial Sloan Kettering Cancer Center
L group lesion: Both ECD and LCH
Inflammatory myeloid neoplasms?

• **BRAF-V600E** expressed in lesional cells along w/ BM progenitor cells and circulating monocytes/myeloid DC*

• Gene expression profiles may still support their divergent morphology/immunophenotype
  – LCH from dendritic cells
  – ECD from monocytes


*Collin M. Pediatric Blood & Cancer. 2016; 63(S2):S15
33rd annual Histiocyte Society meeting  
Singapore October 2-4, 2017

- Become a member of the Histiocyte Society!  
  - https://histiocytesociety.org

- The North American Consortium for Histiocytosis (NACHO) is the first Multi-Institutional consortium in North America with a solid scientific agenda and the research infrastructure necessary for the development and effective implementation of clinical and translational studies and biological research for histiocytic diseases.  
  - http://www.nacho-consortium.org/

- The steps to join NACHO and open the LCH-IV are outlined:  
International Rare Histiocytic Disorders Registry (IRHDR)

• JXG family, ECD, Multifocal Reticulohistiocytosis, RDD and the Malignant lesions of histiocytic phenotype
  
  https://clinicaltrials.gov/ct2/show/NCT02285582

• More information on HS website:
  
  http://histiocytesociety.org/main-website-pages/clinical-trials/clinical-studies/IRHDR