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

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Learning objectives
1. Understand that histiocytic neoplasms are heterogeneous with overlapping features and an unifying diagnosis requires:
   - Pathology: MIP
     - Morphology, Immunophenotype, Pattern of involvement
   - Clinical and Radiographic findings
2. Review updates to the classification scheme...
   - Pathogenesis: Inflammatory myeloid neoplasms?
   - Mixed histiocytic lesions
   - Molecular updates

Contemporary Classification of Histiocytic Disorders

- Macrophage-related
  - Lymphatic histiocytosis
  - Macrophage-related histiocytosis
  - Lymphoplasmacytic lymphoma
- Neoplastic
  - Langerhans cell histiocytosis
  - Neurofibromatosis
  - Secondary hemophagocytic syndrome
  - Myelofibrosis
- Others
  - Rosai-Dorfman disease
  - Sinus histiocytosis with massive lymphadenopathy
  - Solitary histiocytoma with macrophage phenotype
The World Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues

Update:
• Histiocytic sarcoma
• Tumors derived from Langerhans cells
• Interdigitating dendritic cell sarcoma
• Follicular dendritic cell sarcoma
• Other rare dendritic cell tumors:
  • Indeterminate dendritic cell tumor
  • Fibroblastic reticular cell tumor
• Disseminated juvenile xanthogranuloma (ECD)
• Not covered: Reticulohistiocytosis and Rosai-Dorfman Disease —> WHO Classification of Tumours of Skin

Table 5. Histiocytic and dendritic-cell neoplasms.

<table>
<thead>
<tr>
<th>Category</th>
<th>Subtypes and Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage/histiocytic neoplasms</td>
<td>Histiocytic sarcoma</td>
</tr>
<tr>
<td>Dendritic-cell neoplasms</td>
<td>Langerhans cell histiocytosis</td>
</tr>
<tr>
<td></td>
<td>Langerhans cell sarcoma</td>
</tr>
<tr>
<td></td>
<td>Interdigitating dendritic cell sarcoma/tumor</td>
</tr>
<tr>
<td></td>
<td>Follicular dendritic cell sarcoma/tumor</td>
</tr>
<tr>
<td></td>
<td>Dendritic cell sarcoma, not otherwise specified (NOS)</td>
</tr>
</tbody>
</table>

WHO classification of tumours of haematopoietic and lymphoid tissues

2008 Update:
• Histiocytic sarcoma
• Tumors derived from Langerhans cells
• Interdigitating dendritic cell sarcoma
• Follicular dendritic cell sarcoma
• Other rare dendritic cell tumors:
  • Indeterminate dendritic cell tumor
  • Fibroblastic reticular cell tumor
• Disseminated juvenile xanthogranuloma (ECD)
• Not covered: Reticulohistiocytosis and Rosai-Dorfman Disease —> WHO Classification of Tumours of Skin

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Table 2. Highlights of changes in 2016 WHO classification of lymphoid, histiocytic, and dendritic neoplasms

<table>
<thead>
<tr>
<th>Category</th>
<th>Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erdheim-Chester disease</td>
<td>Should be distinguished from other members of</td>
</tr>
<tr>
<td></td>
<td>the juvenile xanthogranuloma family</td>
</tr>
<tr>
<td></td>
<td>Often associated with BRAF mutations</td>
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<tr>
<td>Other histiocytic/dendritic</td>
<td>Clonal relationship to lymphoid neoplasms</td>
</tr>
<tr>
<td></td>
<td>recognized in some cases</td>
</tr>
</tbody>
</table>

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

A Group:
- LCH
- LGD
- CD7
- HOECHST

B Group:
- Langerhans cell histiocytosis (LGD)
- Erdheim-Chester Disease (ECD)

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

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

M Group:
- Primary Malignant Histiocytoses
- Secondary Malignant Histiocytoses (following or associated with another hematologic neoplasm)
  - Subtypes: Histiocytic, interdigitating, Langerhans, Indeterminate Cell
**Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages**

**BLOOD, 2 JUNE 2017 · VOLUME 127, NUMBER 22**

**Taken out of the classification (mesenchymal origin):**

- Follicular Dendritic Cell Sarcoma: FDC (CD21, CD23, CD35)
- Fibroblastic reticular cell tumor: Interstitial reticulum cell (CK, actins)

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**Langerhans cell histiocytosis (LCH)**

- **MIP**: $CD1a \neq LCH$
  - LCH vs Dendritic cell/Langerhans cell hyperplasia
  - Pattern of involvement is important
- **Updates to proposed classification**
  - Myeloid inflammatory neoplasia
  - BRAF and beyond
  - ”L” Group
    - LCH
    - Mixed LCH/ECD
    - ECD (Erdheim Chester Disease)
    - ICH (Indeterminate cell histiocytosis)

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*Children's National Medical Center*

*UPMC*
Pattern of Nodal LCH – Sinus Disease

CD1a
CD207

LCH?

Dendritic cell hyperplasia - Not LCH

CD1a
CLL with dendritic cell (DC) hyperplasia

Not LCH

Bone marrow LCH

BM LCH?

Myeloid inflammatory neoplasia

• LCH distinct gene expression profile from skin LC
• In vivo animal models and human studies
  – LCH is derived from immature myeloid dendritic cells of the bone marrow (BM)
  – Clinically distinct LCH groups defined by:
    • BRAF-V600E mutation within CD34+ BM progenitor cells and circulating CD11c+CD14+ cells (MS-LCH) versus only in tissue restricted CD207+ dendritic cells (SS-LCH).
    • "Misguided myeloid differentiation model; "Mutations in the MAPK/ERK pathway at critical stages in myeloid differentiation appear to be an essential and universal driver of LCH pathology and clinical phenotypes"

**BRAF Prognostic Marker?**

**BRAF Mutation Correlates with High-Risk LCH and Increased Resistance to First-Line Therapy**


Higher reactivation rate (5-year)
  – 42.8% v. wt 28.1%; P = .006
• Increased resistance to combined vinblastine and corticosteroid Rx
  – 21.9% v. wt 3.3%; P = .001
• Higher Rate of permanent consequence (including DI, ND-LCH)
  – 27.9% and wt 12.6%; P = .001

**BRAF and beyond ...LCH**

• 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, MAP3K1
• BRAF exon 12 in-frame deletions*
• FAM73A-BRAF gene fusion*

*Allen CE, Parsons DW. Hematology Am Soc Hematol Educ Program. 2015;2015:559-64.
**Diverse Kinase Alterations in LCH:**

![Image of kinase alterations]

Lee et al. JCI Insight 2017**

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**Future tools...**

**BRAF-V600E testing in circulating peripheral blood cells/BM (CLIA approved*) and/or cell free DNA**


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**“L” group**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Subtypes</th>
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<tbody>
<tr>
<td>LCH</td>
<td>LCH SB, LCH MS, LCH MS-RD, LCH MS-RD</td>
</tr>
<tr>
<td>ICH</td>
<td>ECD, ECD classical type, ECD without bone involvement, ECD with another myeloproliferative/myelodysplastic disorder, Extramedullary or disseminated JX with MAPK</td>
</tr>
</tbody>
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**Mixed ECD and LCH**

ECD, Erdheim-Chester disease; ICH, indeterminate cell histiocytosis; LCH, Langerhans cell histiocytosis; NS, multiple system; RD, risk organ; SB, single system.


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


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**Original skin biopsy of LCH, later shown to also be VE1+**


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**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)

*CD68+ Xanthomatous histiocytes ≠ ECD

ECD with pericardial and pleural effusions

ECD with brain involvement

**ECD = Clinical, Radiographic, and Pathologic**

**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**


**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


**“L” group: Systemic JXG with mutations**

<table>
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<th>Table 1. Histiocytes of the L group</th>
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<td>Most ECD and LCH</td>
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**Update on Xanthogranuloma family**

Growing molecular understanding:

- Chakraborty et al 2014 – 3 of 4 systemic or disseminated cutaneous JXG harbored 8-9 somatic mutations in various chromosomes, PI3KCD mutation and germline NF1 mutation
- Diamond and Durham et al 2016 – 8 of 12 (67%) systemic JXG harbored MAPK pathway mutations

**Growing molecular understanding:**

Systemic JXG 67% (n=12) with MAPK pathway alterations

- Wild Type 33%
- NRAS/ARAF* 17%
- KRAS 17%
- MAP2K1 25%

*Concurrent NRAS and ARAF mutation in same lesions

Systemic ALK+ histiocytosis in infancy

- **TPM3-ALK fusion**
  - Positive: ALK, CD163, CD68, lysozyme, and variable fascin, Factor 13a and S100
  - Negative: CD30, CD1a and CD207
- Chan et al 2008; 3 female infants
  - Hepatosplenomegaly with bland sinusoidal histiocytic infiltrates
  - Differential diagnosis: Storage disease
  - Clinical resolution ...An unique but self-limited form of systemic histiocytosis of infancy?

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**“L” group**

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ICH: Indeterminate cell histiocytosis

- ECD: Eosinophilic Chester disease
- EOD: Eosinophilic osteomyelofibrosis
- Associated with another myeloproliferative disorder

**L group:** Indeterminate cell histiocytosis (ICH)

- Molecular Update: **ETV3-NCOA2**
- Orphan L-group lesion
- Langerhans-like DC: CD1a+/S100-; Lacks Birbeck granules (Langerin-)
- LCH can have sparse Birbeck granules /Langerin
- Adults, solitary or multiple skin lesions

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**ICH with ETV3-NCOA2**

- CD1a+, CD207- /+ w/ Intermediate phenotype

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**M group:** Malignant neoplasms of the histiocytic phenotype

- Malignant cytomorphology:
  - Pleomorphism, increased mitoses, ± atypical mitoses
- Updates to proposed classification
- Primary malignancies of the histiocytic phenotype
  - Re-grouping into “M” group: Histiocytic sarcoma (HS), Langerhans cell sarcoma (LCS), interdigitating cell sarcoma/tumor (IDCS), and indeterminate cell sarcoma
  - Out: Follicular Dendritic Cell Sarcoma/Fibroblastic reticular cell tumor
  - Molecular: BRAF and beyond
    - BRAF-V600E, HRAS, CLIP2-BRAF, BRAF-V599L w/ HRAS,
    - PTER mutation
  - Secondary malignancies of histiocytic phenotype
    - Share common molecular signature of the primary malignancy
Malignant cytomorphology

Langerhans cell sarcoma

Overlapping features: M group: LCS? HS?

CD1a+, CD163+

CD1a+, CD68+

Ki-67

Secondary histiocytic lesions following Prior hematopoietic malignancy

- Secondary histiocytic malignancy (HS) following:
  - B and T-cell acute lymphoblastic leukemia (ALL)
  - Non-Hodgkin lymphomas (Follicular, CLL, HCL)
- Secondary “atypical histiocytic neoplasms, NOS” following:
  - B and T-cell ALL
  - Acute myeloid leukemia (JXG-like lesion with shared inv16)
  - Diffuse large B-cell lymphoma (Lesion with mixed LCH/JXG/RDD phenotype with BRAF-V600E)


Rosai-Dorfman Disease (RDD)

- MIP—Alone emperipolesis, S100+ ≠ RDD
  - Morphology: Large cells, pale cytoplasm
  - Variable emperipolesis, plasma cells, fibrosis
  - IHC: S100, fascin, CD68, variable CD163 and CD14
  - Pattern of involvement (Lymph node: Sinus disease)

- Updates to proposed classification
  - "R" group lesion
    - Sporadic RDD
    - Related conditions predisposing to RDD
  - While no BRAF, other MAPK pathway mutations found

R group: RDD updates

- Autoimmune, Genetic, Neoplasia Related:
  - Increased IgG4 and RDD...?
  - Histiocytosis-Lymphadenopathy plus syndrome (e.g. Faisalabad histiocytosis) with a homozygous or compound heterozygous mutation in the solute carrier family 29, SLC29A3 gene (OMIM #602782)
  - Autoimmune lymphoproliferative syndrome (ALPS), type I with heterozygous germline mutation in TNFRSF6, the FAS gene (OMIM#601859)
  - Concurrent lymphoma or LCH

- Molecular updates:
  - NRAS, KRAS, and ARAF
Growing molecular understanding: Sporadic RDD 44% (n=9) with MAPK pathway mutations

- NRAS 11%
- ARAF 11%
- WT 56%
- KRAS 22%

*Unlike systemic JXG, No concurrent NRAS and ARAF mutation in same lesion

Conclusions

1. Pathology of histiocytic neoplasms can be heterogenous
   - MIP* with clinical and radiographic findings
     - Morphology, Immunophenotype, Pattern of involvement
2. Updates to the classification scheme:
   - LCH/ECD: Pathogenesis emerging as an inflammatory myeloid neoplasm
   - Mixed histiocytic lesions still not defined but ever more recognized
   - Malignant lesions of histiocytic phenotype:
     - Moving away from sarcoma designation while understanding phenotype heterogeneity and in secondary lesions: a shared clonality
   - MAPK pathway mutations important in histiocytic lesions:
     - Targetable kinases playing increasing role in treatment
     - Pathogenesis, Diagnosis, and Prognostic implications

“H” group

- Hemophagocytosis lymphohistiocytosis (HLH):
  ≠ Histiocytic disorder; ≠Immunoregulatory disorder
- HLH may be associated with histiocytic lesions
  - LCH and HLH in liver
- Updates to “H” group
  - Primary
    - New genetic entities: NLRC4 inflammasome
  - Secondary
    - Rheumatologic HLH: Best named as “MAS-HLH”
    - Mutations in 2° HLH with Partial cytolytic dysfunction

Collaborators:

- Dr. Ronald Jaffe
- Lori Schmitt
- Dr. Nathanael Bailey
- Dr. Carl Allen
- Dr. Ken McClain
- Dr. Rikha Chakraborty

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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:
References*


THANK YOU