Saja Asakrah, MD Ph.D
Disclosure

• No conflict of interest to disclose
Case #13 A 44 year old male with no past medical history presented with a painless slowly growing lump in front of his left ear that he noticed one year prior.
Histiocytes

- Cell of origin and classification
- Reactive versus clonal/neoplastic histiocytic infiltrate
- Malignant histiocytic infiltrate (sarcoma)
- Associated with hematopoietic or non hematopoietic lesions
Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

**L 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 Lymphoma, 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 FKRC43A mutated patients have concomitant BRAFV600E mutations.

Figure 1. Histology and somatic mutations of histiocytoses of group L, C, R, M, and H. (A) L group: Histology of LCH (skin [i-ii] and bone [iii]) and of ECD (perirenal [iv-v]). Pie chart of relative frequencies of activating kinase mutations in LCH (vi) and ECD (vii). (B) C group: Histology of JXG (i-ii). (C) R group: Histology of RDD (meningeal with high IgG4+ plasma cell infiltration [i-ii]). (D) M group: Histology of MNL (i-ii). (E) M group: Histology of Inherited HLH (river [i-ii]). Staining with CD1a (Lil in red), IgG4 (Pil in brown), CD163 (Lil in brown), or hematoxylin and eosin (all others). NOS, not otherwise specified.
<table>
<thead>
<tr>
<th>Cell type</th>
<th>origin</th>
<th>markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erdheim-Chester disease (Macrophages)</td>
<td>Bone marrow- myeloid progenitor</td>
<td>CD68, CD4, CD14, <strong>CD163</strong>, CD11c, S100 staining has been reported</td>
</tr>
<tr>
<td>Indeterminate cell histiocytosis</td>
<td>Unclear cell of origin</td>
<td>CD68, CD4, S100, MHC-II, CD1a</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis (langerhans cells)</td>
<td>Yolk sac- embryonal liver Bone marrow derived-myeloid progenitor</td>
<td>CD68, CD4, MHC-II, S100, <strong>CD1a</strong>, Langerin (CD207).</td>
</tr>
</tbody>
</table>
Classic morphology of Langerhans cell histiocytosis involving a lymph node
A case of Erdheim-Chester disease involving tibia
Histiocytes

<table>
<thead>
<tr>
<th>Cell of origin and classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive versus clonal/neoplastic histiocytic infiltrate</td>
</tr>
<tr>
<td>Malignant histiocytic infiltrate (sarcoma)</td>
</tr>
<tr>
<td>Associated with hematopoietic or non hematopoietic lesions</td>
</tr>
</tbody>
</table>
Dermatopathic lymphadenopathy
Reactive histiocytosis in a left neck mass core biopsy
CD1a

Cytokeratin AE1/AE3

Dx Nasopharyngeal carcinoma

EBV ISH
In challenging cases mutational analysis may be helpful in supporting a clonal process.
MAPK pathway mutations

- **B-Raf proto-oncogen:**
  
  In contrast to recurrent BRAF V600E mutations, other mutations in BRAF have been found only rarely in histiocytoses. These include BRAF V600D and BRAF V600insDLAT in LCH, BRAF F595L in histiocytic sarcoma.

- **A-Raf Proto-oncogen:**
  
  Recurrent in non-LCH and are present in 21% of ECD.

- **RAS isoforms:**
  
  This includes NRAS mutations in 3–7% of ECD and less frequently in LCH.

- **MAP2K1:**
  
  Recurrent in LCH and are present in 10–40% of LCH patients. MAP2K1 mutations are also present in non-LCH and occur in 14% of ECD.

- **PI3K mutation:**
  
  Activating PIK3CA mutations have been described in 17% of BRAF V600E-wildtype ECD.
<table>
<thead>
<tr>
<th>CDx or LDT</th>
<th>THxID-BRAF kit</th>
<th>cobas 4800 BRAF V600 mutation test</th>
<th>Sanger</th>
<th>HRM</th>
<th>Pyrosequencing</th>
<th>IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, %</td>
<td>&gt;96 for V600E; &gt;92 for V600K</td>
<td>~97 for V600E; 66–70 for V600K</td>
<td>92–98</td>
<td>98–100</td>
<td>&gt;98</td>
<td>85–100</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>100</td>
<td>&gt;98</td>
<td>100</td>
<td>98–100</td>
<td>90–100</td>
<td>98–100</td>
</tr>
<tr>
<td>Limit of detection, %</td>
<td>5 for V600E, V600K</td>
<td>5–7 for V600E; &gt;35 for V600K</td>
<td>6.6</td>
<td>6.6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Mutations detected</td>
<td>Approved for V600E, V600K</td>
<td>Approved for V600E only</td>
<td>99% of all detectable mutations</td>
<td>99% of all detectable mutations</td>
<td>Assay optimized for V600 mutations is available</td>
<td>VE1 antibody specific for V600E</td>
</tr>
<tr>
<td>Sample</td>
<td>Tumor-derived DNA</td>
<td>Tumor-derived DNA</td>
<td>Tumor-derived DNA</td>
<td>Tumor-derived DNA</td>
<td>Tumor-derived DNA</td>
<td>Tissue</td>
</tr>
<tr>
<td>Cost</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>
Cyclin-D1 staining in LCH

Cyclin D1 (brown) and CD1a (pink)

TABLE 2. Summary of Cyclin D1 Expression by Langerhans Cell Histiocytosis and Reactive/Normal Langerhans Cells

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cyclin D1&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langerhans cell histiocytosis</td>
<td>39/39 (100)</td>
</tr>
<tr>
<td>Expression in &gt; 20% Langerhans cells</td>
<td>33/39 (85)</td>
</tr>
<tr>
<td>Expression in 5%-20% of Langerhans cells</td>
<td>6/39 (15)</td>
</tr>
<tr>
<td>Dermatopathic lymphadenitis</td>
<td>0/19 (0)</td>
</tr>
<tr>
<td>Dermatitis (with Langerhans cell microabscesses)</td>
<td>4*/18 (22)</td>
</tr>
<tr>
<td>Normal skin</td>
<td>0/12 (0)</td>
</tr>
</tbody>
</table>

<sup>*Rare, scattered CD1a<sup>+</sup> cells (5% to 10%) with cyclin D1 expression were observed.</sup>
## Histiocytes

### Cell of origin and classification

### Reactive versus clonal/neoplastic histiocytic infiltrate

### Malignant histiocytic infiltrate (sarcoma)

### Associated with hematopoietic or non hematopoietic lesions
Langerhans cell histiocytic sarcoma
Histiocytes

Cell of origin and classification

Reactive versus clonal/neoplastic histiocytic infiltrate

Malignant histiocytic infiltrate (sarcoma)

Associated with hematopoietic or non hematopoietic lesions
### Table 1 Reported cases of histiocytic sarcoma as a secondary malignancy.

<table>
<thead>
<tr>
<th>Author</th>
<th>Primary diagnosis</th>
<th>Age at primary diagnosis (years)</th>
<th>Age at HS diagnosis (years)</th>
<th>Interval to HS (months)</th>
<th>FISH analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunner</td>
<td>FL</td>
<td>75</td>
<td>81</td>
<td>72</td>
<td>Bcl2 rearrangement</td>
</tr>
<tr>
<td>Feldman</td>
<td>FL</td>
<td>62</td>
<td>64</td>
<td>24</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Feldman</td>
<td>FL</td>
<td>66</td>
<td>63</td>
<td>14</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Feldman</td>
<td>FL</td>
<td>69</td>
<td>63</td>
<td>72</td>
<td>Bcl2 rearrangement</td>
</tr>
<tr>
<td>Feldman</td>
<td>FL</td>
<td>62</td>
<td>64</td>
<td>24</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Feldman</td>
<td>FL</td>
<td>39</td>
<td>42</td>
<td>36</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Feldman</td>
<td>FL</td>
<td>60</td>
<td>63</td>
<td>32</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Feldman</td>
<td>FL</td>
<td>48</td>
<td>48</td>
<td>7</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Feldman</td>
<td>FL</td>
<td>62</td>
<td>62</td>
<td>7</td>
<td>synchronous NR¹</td>
</tr>
<tr>
<td>Feldman</td>
<td>FL</td>
<td>68</td>
<td>68</td>
<td>7</td>
<td>synchronous NR¹</td>
</tr>
<tr>
<td>Feldman</td>
<td>FL</td>
<td>67</td>
<td>67</td>
<td>7</td>
<td>NR¹</td>
</tr>
<tr>
<td>Wang</td>
<td>FL</td>
<td>44</td>
<td>61</td>
<td>204</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Zeng</td>
<td>FL</td>
<td>43</td>
<td>47</td>
<td>48</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Feldman</td>
<td>B-ALL</td>
<td>14</td>
<td>16</td>
<td>24</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Wang</td>
<td>SMZL</td>
<td>62</td>
<td>65</td>
<td>12</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Castro</td>
<td>T-ALL</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>McCune</td>
<td>B-ALL</td>
<td>25</td>
<td>26</td>
<td>4</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Boubadjah</td>
<td>B-ALL</td>
<td>24</td>
<td>26</td>
<td>35</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Castro</td>
<td>B-ALL</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Oriciu</td>
<td>B-ALL</td>
<td>14</td>
<td>16</td>
<td>24</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Oriciu</td>
<td>B-ALL</td>
<td>13</td>
<td>13</td>
<td>3</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Kumar</td>
<td>B-ALL</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>CDKN2A del</td>
</tr>
<tr>
<td>Mori</td>
<td>CMML</td>
<td>79</td>
<td>70</td>
<td>synchronous</td>
<td>Monocloning signal</td>
</tr>
<tr>
<td>Song</td>
<td>MCTC</td>
<td>16</td>
<td>16</td>
<td>0</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Zhang</td>
<td>FLCL/LBCL</td>
<td>50</td>
<td>50</td>
<td>synchronous</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Bassecaoa</td>
<td>FLCL/LBCL</td>
<td>53</td>
<td>60</td>
<td>150</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Bassecaoa</td>
<td>DLBCL</td>
<td>63</td>
<td>64</td>
<td>12</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Shao</td>
<td>CLL</td>
<td>85</td>
<td>85</td>
<td>synchronous</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Hue</td>
<td>MCL</td>
<td>58</td>
<td>60</td>
<td>24</td>
<td>CCND1/GH</td>
</tr>
<tr>
<td>Michonneau</td>
<td>HCL</td>
<td>48</td>
<td>74</td>
<td>312</td>
<td>NR¹</td>
</tr>
<tr>
<td>Zhao</td>
<td>AMoL</td>
<td>62</td>
<td>62</td>
<td>synchronous</td>
<td>NR¹</td>
</tr>
<tr>
<td>Alvaro</td>
<td>MALT Lymphoma</td>
<td>52</td>
<td>52</td>
<td>synchronous</td>
<td>NR¹</td>
</tr>
<tr>
<td>Anseri</td>
<td>CML</td>
<td>69</td>
<td>71</td>
<td>39</td>
<td>BCR-ABL¹</td>
</tr>
</tbody>
</table>

---

**Secondary Histiocytic Neoplasm**

---

*European Journal of Haematology, 97(1), 9-16*
What’s the likely diagnosis?

A- Reactive dermatopathic lymphadenopathy

B- Langerhans cell histiocytosis

C- Langerhans cell sarcoma

- Morphologic atypia
- Ki67 proliferation fraction
- Distribution pattern
- Cyclin-D1 staining
Reference


Questions