Langerhans Cell Histiocytosis (LCH)
- **Definition:** Neoplastic proliferation of Langerhans cells
- More common in children, male, white
- Single lesion, multiple lesions, or disseminated and multisystem
- Most commonly involves bone (single or multiple lytic bone lesions), followed by lymph node (sinusoidal involvement), skin, lung, liver/spleen
- **Morphology:** Very characteristic morphology known as “coffee bean”: oval, grooved, folded, indented, or lobed nuclei. Eosinophils always present (formerly called: eosinophilic granuloma). Occasional Charcot-Layden crystals if eosinophilic abscess present.
- **Electronmicroscopy:** Birbeck granules (tennis racket shaped granules) - hallmark
- **Phenotype:** CD1a+, S-100+, Langerin+ (stain Birbeck granules), CD68 variable, dim, BRAF+ (subset)
- **Genetics:** BRAF V600E mutated 50%. MAP2K mutation 25% (mutually exclusive)
- **Prognosis:** Good prognosis in unifocal disease, worse in multisystem disease and when accompanied by other hematopoietic neoplasms
- **Differential:** Rosai-Dorfman disease (Histiocytic proliferation with emperipolesis, CD68+, S-100+, CD1a-, not a malignant disease)

Langerhans Cell Sarcoma
- Skin most common, multi-organ involvement
- Cells have more atypical morphology (may lose “coffer bean” shape), increased mitosis, absent eosinophils
- Phenotype identical to LCH, but expresses CD56. Proliferation rate usually >50
- Prognosis: Aggressive high grade malignancy

Rosai-Dorfman Disease (Sinus Histiocytosis with Massive Lymphadenopathy)
- **Definition:** Proliferation of reactive histiocytes and plasma cells resulting in enlargement of lymph nodes or soft tissue causing space occupying symptoms
- More common in children and young adult male
- Usually single painless lesion, cervical most common, may also affect other lymph nodes and extranodal tissue (skin, subcutaneous tissue, orbit, bone, CNS)
- Often associated with fever, high ESR, polyclonal hypergammaglobulinemia
- **Morphology:** Enlarged lymph node with expanded sinuses containing numerous histiocytes
  - Histiocytes are large in size with small bland-appearing nuclei
  - Cytoplasm contains engulfed, but intact cells (emperipolesis - hallmark)
  - Numerous mature plasma cells between the sinuses (alternating “light” and “dark” banding pattern)
- **Phenotype:** CD68+, S-100+, CD1a-
- **Genetics:** No known genetic changes, non-clonal
- **Prognosis:** Spontaneous regression or protracted course. Treated by surgery and in some patients by steroids
- **Differential:** Reactive lymph node with increased histiocytes in sinuses, other histiocytic lesions
**Histiocytic Sarcoma**

Definition: Malignant neoplasm of histiocytes  
Very rare disease  
Affects adults of all ages  
May involve lymph nodes or extranodal sites, may follow a previous leukemia  
May be accompanied by B symptoms  
**Morphology:** Tumor cell morphology varies, ranging from slightly atypical to large bizarre nuclear features. A large amphophilic nucleolus. Cell shapes are stubby oval, to spindle, to epithelioid, with abundant cytoplasm  
**Phenotype:** CD68+, S-100-/+ , CD1a-, CD45+, CD14+, Lysosome+  
**Genetics:** Unknown  
**Prognosis:** Single lesion is mostly indolent. High stage disease has poor prognosis  
**Differential:** Other histiocytic lesions

**Follicular Dendritic Cell Tumor and Sarcoma**

Definition: Benign or malignant neoplasm of follicular dendritic cells  
Very rare disease  
Affects adults of all ages  
May involve lymph nodes or extranodal sites, cervical lymph node and mediastinum most common. Extranodal sites include skin, soft tissue, tonsil, GI  
May arise from hyaline vascular Castleman disease  
**Morphology:** Highly cellular spindle cell morphology, may be in whirling pattern  
- Cell shape from elongated, to plump, to ovoid  
- Oval shaped nuclei, with variable degree of pleomorphism, and a small nucleolus  
**Phenotype:** CD21+, CD23+, CD35+, CD68+, S-100-, CD1a-  
**Genetics:** Unknown  
**Prognosis:** Low grade lesions are indolent and treated by surgery. High grade, organ based lesions more aggressive in course  
**Differential:** Other histiocytic lesions

**Interdigitating Dendritic Cell Sarcoma**

Definition: Malignant neoplasm of interdigitating dendritic cells  
Very rare disease  
Affects adults of all ages  
May involve lymph nodes or extranodal sites (nasopharynx, intestine, retroperitoneum, mesentery, testes)  
May be accompanied by B symptoms  
**Morphology:** Spindle cell morphology predominant, forms fascicles and whirls. Round or oval shaped cells may be seen. Round or oval nuclei with a small nucleolus.  
**Phenotype:** S100+, CD68-, CD1a-, CD21-, CD35-  
**Genetics:** Unknown  
**Prognosis:** Mostly aggressive with 50% mortality. Localized lesion has better outcome  
**Differential:** Other histiocytic lesions
## Rare histiocytic and dendritic lesions

<table>
<thead>
<tr>
<th>Histiocytic sarcoma</th>
<th>Follicular dendritic cell sarcoma</th>
<th>Interdigitating dendritic cell sarcoma</th>
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<tbody>
<tr>
<td>Malignant</td>
<td>Benign or malignant</td>
<td>Malignant</td>
</tr>
<tr>
<td>Affect adults of all age</td>
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</tr>
<tr>
<td>Lymph nodes and extranodal sites</td>
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</tr>
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