## Histiocytosis

**Amy Reinstadler, M.D.**

### Langerhans cell histiocytoses

<table>
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<tr>
<th>Histiocytosis</th>
<th>Age group</th>
<th>Most common mucocutaneous sites</th>
<th>Other findings</th>
<th>Histology</th>
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</table>
| **Letterer–Siwe**                    | Young infants (<2 years) | Scalp, face trunk, buttocks (resembles seborrheic dermatitis) | • Visceral and bone lesions  
• More fulminant course  
• Fever, anemia, lymphadenopathy  
• Hemorrhagic component may resemble blueberry muffin baby | Langerhans cells (reniform nuclei; may be foamy or resembles Touton histiocytes) with epidermotropism; mixed infiltrate (+ mast cells)  
Birbeck granules on electron microscopy |
| **Hand–Schüller–Christian**          | Children beyond infancy | May resemble Letterer–Siwe or may be papulonodular or granulomatous ulceration in intertriginous areas | • Diabetes insipidus  
• Bone lesions (skull)  
• Exophthalmos. | Less epidermotropism, more foamy cells, more giant cells |
| **Eosinophilic granuloma**           | Older children and young adults | Skin lesions rare. Nodulo-ulcerative lesions in mouth, perineal, perivulval, or retroauricular | Bone lesions primarily; more benign course | |
| **Congenital self-healing reticulohistiocytosis (Hashimoto–Pritzker disease)** | Congenital | Widespread, localized, or single lesion | Spontaneous resolution in several months; usually no systemic disease |  
+/- Birbeck granules on electron microscopy |

### Non-Langerhans cell histiocytoses

#### Cutaneous, self-resolving

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| **Juvenile xanthogranuloma**         | Young infants (<75% occur in 1st year of life) | - Head and neck  
> upper trunk  
> extremities  
- Small nodular form, multiple 2–5 mm papules  
- Large nodular form, one or few 1-2 cm nodules | • Rare eye and visceral lesions; can lead to blindness  
• Oral JXG is rare; usually on lateral tongue or midline of the hard palate  
• When associated with NF1, 20x increased risk of developing juvenile myelomonocytic leukemia |  
**Dendritic cell marker:**  
Factor XIIIa+  
**Macrophage markers:**  
CD68+  
HAM56+/-(+)  
Mac387+/-  
**Langerhans cell markers:**  
CD1a-  
S100-  
CD34-  
Diffuse dermal non-foamy histiocytes with sparse lymphocytes and eosinophils |
| **Benign cephalic histiocytosis**    | Young infants | Face and neck  
Usually none, spontaneous resolution | |  
**Langerhans cell markers:**  
CD68-  
CD1a-  
S100-  
CD34-  
Circumscribed dermal nodule with oncocytic mononuclear histiocytes, multinucleate giant cells with ground glass cytoplasm |
| **Reticulohistiocytoma**             | Adults | Head (solitary lesion) | None |  
**Langerhans cell markers:**  
CD1a-  
S100-  
CD34-  
Superficial and mid dermis with a uniform infiltrate of histiocytes and a few lymphocytes |
| **Generalized eruptive histiocytosis** | <4 and adults | Widespread (axial); occasional mucosal involvement in adults | Spontaneous resolution |  
**Immunophenotypic profile:**  
Antigenic markers of both LCH (S100+, CD1a+) and non-LCH (CD68+; Factor X111a+, HAM56+)  
No Birbeck granules |
| **Indeterminate cell histiocytosis** | Adults and children | Widespread > face and neck | • Uncommon visceral and bone lesions  
• Ocular involvement has been described.  
• Usually self limited | No Birbeck granules |

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### Histiocytosis (continued)

**M. Amy Reinstadler**, M.D.

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<td><strong>Cutaneous, persistent/progressive</strong></td>
<td></td>
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<tr>
<td>Papular xanthoma</td>
<td>Any</td>
<td>Generalized; occasionally on mucous membranes</td>
<td>None. Affected individuals are usually normolipidemic</td>
<td>Factor XIIIa +, CD68 +, HAM56 +, Foamy macrophages and Touton giant cells. No chronic inflammatory cells</td>
</tr>
<tr>
<td>Progressive nodular histiocytoma</td>
<td>Any</td>
<td>Nodules on trunk and papules widespread (including genitals)</td>
<td>Normolipidemic</td>
<td>Histiocytes, foam cells, spindled cells</td>
</tr>
<tr>
<td><strong>Cutaneous with frequent systemic involvement</strong></td>
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| Necrobiotic xanthogranuloma | Teens to adults | Periorbital > trunk, extremities | Paraproteinemia, heparosplenomegaly, lymphoproliferative disease | • Broad zones of hyaline necrobiosis and granulomatous foci composed of histiocytes, foam cells, and multinucleate giant cells (Touton and foreign body type).  
• Cholesterol clefts may be present |
| Multicentric reticulohistiocytosis | Adults (usually >30) | Head, hands, fingers (‘coral bead’ appearance periungually), ears, and articular regions of the limbs; mucosa (oral, nasopharyngeal) | • Arthritis (often destructive)  
• Up to 30% with internal malignancy  
• Assoc with hyperlipidemia  
• PPD, systemic vasculitis, and autoimmune disease | • Nodular infiltrate of histiocytes with ground glass cytoplasm.  
• Bizarre multinucleated giant cells  
• Mixed infiltrate  
• CD68+, S100- |
| Rosai–Dorfman disease | Kids and young adults | Eyelids and malar area | Massive lymphadenopathy in a subset of patients, fever, hyper-gamma-globulinemia | • Affected lymph nodes with dilated sinuses containing neutrophils, lymphocytes, plasma cells, and histiocytes with large vesicular nuclei and abundant cytoplasm  
• Cutaneous lesions with dense dermal infiltrate of histiocytes with scattered lymphocytes, plasma cells and neutrophils  
• Emperipolesis  
• S100+, CD68+, CD1a- |
| Xanthoma disseminatum | Young adults, children | Flexural areas to widespread > mucosa (oral, nasopharyngeal) | Diabetes insipidus, osteolytic bone lesions. Normolipemic | • Histiocytes, foam cells, spindle cells, Touton cells, and a moderate number of chronic inflammatory cells  
• CD68+, factor XIIIa +, S100-, CD1a- |
| **Systemic with rare cutaneous involvement** | | | | |
| Erdheim–Chester disease | Usually adults but can be any age | Dermal and subQ nodules, xanthelasmas, intertrigo-like lesions, pretibial dermopathy, pigmented patches on the lips and mucosa | Primarily a disease of long bones producing patchy medullary scle-rosis with sparing of the epiphyses | • Lipidized histiocytes involve the dermis, often with extension into the subcutis  
• CD68+, factor XIIIa+, CD1a−, and S100−  
• Touson giant cells |
| Hemophagocytic lymphohistiocytosis | Usually in infancy/early childhood but can be any age | Jaundice and non-specific morbilliform rash | Fever, splenomegaly, liver dysfunction, cytopenia, hypofibrinogenemia, and tissue hemophago-cytosis | • Non-specific spongiosis and a mild perivascular infiltrate of lymphocytes and histiocytes  
• S100-, CD68- |