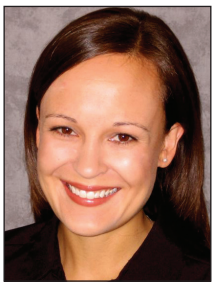
Histiocytosis

Amy Reinstadler, MD (Updated July 2015)*

Histiocytosis	Age group	Most common mucocutaneous sites	Other findings	Histology	
Langerhans cell histiocytoses *(previously Histiocytosis X)*					
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 resemble Touton histiocytes) with epidermotropism; mixed infiltrate (+mast cells) Birbeck granules on electron microscopy S100+ CD1a+ CD68-	More epidermotropism, fewer foamy cells
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		Less epidermotropism, fewer foamy cells, more diffuse infiltrate with eosinophils, histiocytes, and giant cells
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					
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[1]	*Dendritic cell marker:* Factor XIIIa+ *Macrophage markers:* CD68+ HAM56+/- Mac387 +/- *Langerhans cell markers:* CD1a- S100- CD34-	• Nodular or diffuse infiltrate of histiocytes, lymphocytes, and eosinophils (early) • Foamy histiocytes and Touton giant cells (late) • Dermoscopy: orange-yellow background with a subtle peripheral erythematous border with linear branched vessels ("setting sun")[2]
Benign cephalic histiocytosis	Young infants	Face and neck	Usually none, spontaneous resolution		Diffuse dermal non-foamy histiocytes with sparse lymphocytes and eosinophils
Reticulohistiocytoma	Adults	Head (solitary lesion)	None		Circumscribed dermal nodule with oncocytic mononuclear histiocytes, multinucleate giant cells with ground glass cytoplasm
Generalized eruptive histiocytosis	<4 and adults	Widespread (axial); occasional mucosal involvement in adults	Spontaneous resolution		Superficial and mid dermis with a uniform infiltrate of histiocytes and a few lymphocytes
Indeterminate cell histiocytosis	Adults and children	Widespread > face and neck	• Uncommon visceral and bone lesions • Ocular involvement has been described • Usually self limited	Immunophenotypic profile–antigenic markers of both LCH (S100+, CD1a+) and non-LCH (CD68+, Factor XIIIa+, HAM56+) No Birbeck granules	



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Histiocytosis	Age group	Most common mucocutaneous sites	Other findings	Histology	
Cutaneous, persistent/progressive					
Papular xanthoma	Any	Generalized; occasionally on mucous membranes	None. Affected individuals are usually normolipidemic	Factor XIIIa+ CD68+ HAM56+	Foamy macrophages and Touton giant cells. No chronic inflammatory cells
Progressive nodular histiocytoma	Any	Nodules on trunk and papules widespread (including genitals)	Normolipidemic		Histiocytes, foam cells, spindled cells
Cutaneous with frequent systemic involvement					
Necrobiotic xanthogranuloma	Teens to adults	Periorbital > trunk, exremities	Paraproteinemia (IgG kappa), hepa- tosplenomegaly, lympho-proliferative 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 (Sinus Histiocytosis with Massive Lymphadenopathy (SHML) H Syndrome[3]	Kids and young adults Mean age ~20	Eyelids and malar area Hyperpigmentation and hypertrichosis (inner thighs and shins)	Massive Lymphadenopathy (most often cervical) in a subset of patients, fever, hyper-gamma-globulinemia LAD, HSM, hearing loss, heart anomalies, hypogonadism, low height, hyperglycemia, hallux valgus	• 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/ xanthomas, intertrigo-like lesions, pretibial dermopathy, pigmented patches on the lips and mucosa	• Primarily a disease of long bones of lower limbs producing patchy medullary sclerosis with sparing of epiphyses • BRAF V600E mutation in 54%	• Lipidized histiocytes involve the dermis, often with extension into the subcutis • CD68+, factor XIIIa+, CD1a−, and S100− +/- Touton 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 hemophagocytosis	• Non-specific spongiosis and a mild perivascular infiltrate of lymphocytes and histiocytes • S100-, CD68+	

References:

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***Reviewed and updated July 2015 by: Alina Goldenberg, MD, Elise Herro, MD, and Sharon Jacob, MD.**