

Canine Histiocytic Neoplasia: An overview
 Fulmer and Mauldin. Can Vet J 2007; 48: 1041 -1050

Histiocytes:

- move through blood as monocytes and develop in tissues into histiocytes of the mononuclear phagocytic system
- APCs in tissues, then migrate to LNs to present antigen to naive T cells
- leukocytes
 - CD34+ stem cell precursors
 - monocyte, macrophage or DC lineage

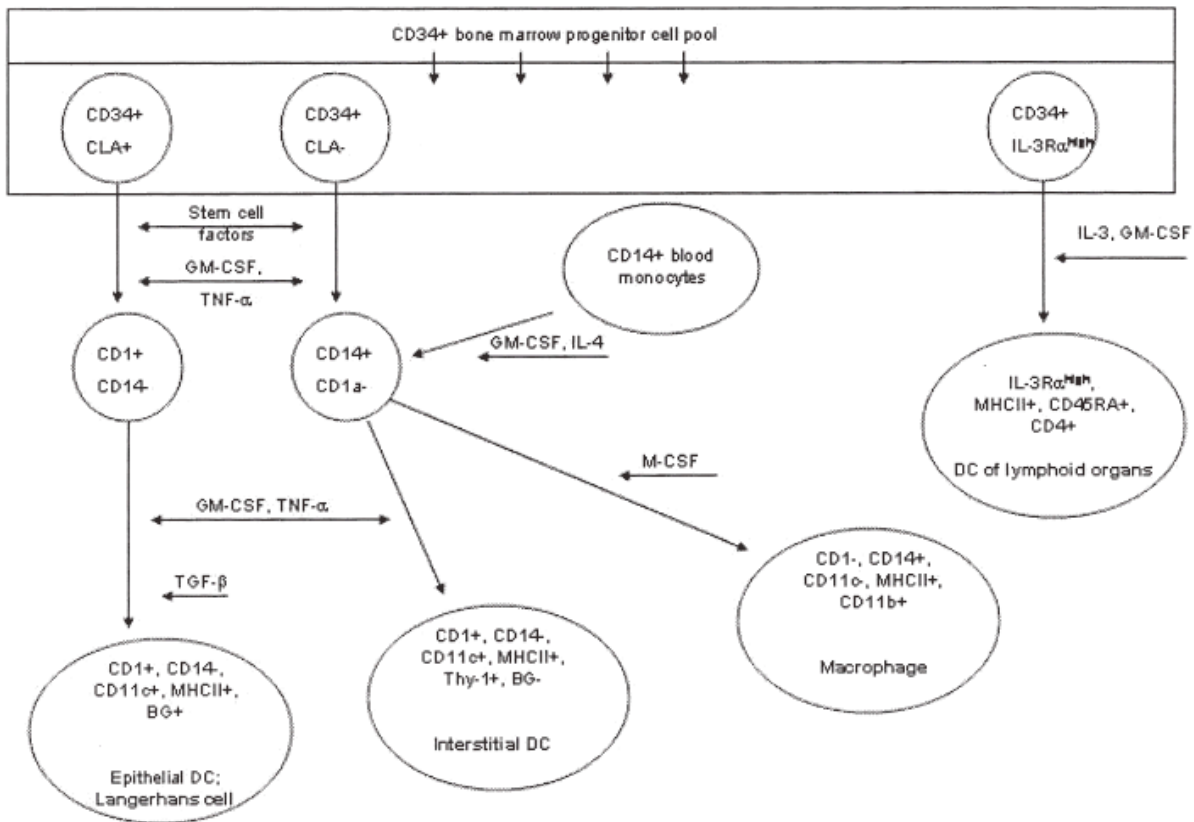


Figure 1. Ontogeny and phenotypic characteristics of myeloid dendritic antigen-presenting cells. DC = dendritic cells; BG = Birbeck's granules. Used with permission, Affolter VK, Moore PF. Localized and disseminated histiocytic sarcoma of dendritic cell origin in dogs. Vet Pathol 2002;39:74–83.

Histiocytic Disorders

3 major categories:

- 1 - canine cutaneous histiocytoma
- 2- canine reactive histiocytoses (cutaneous and systemic)
- 3- histiocytic sarcoma complex (localized and disseminated)
- [4- MFH (soft tissue sarcoma, histiocytic and fibroblastic cell types) NOT HISTIOCYTIC IN ORIGIN but similar morphology to histiocytic sarcoma]

1- canine cutaneous histiocytoma

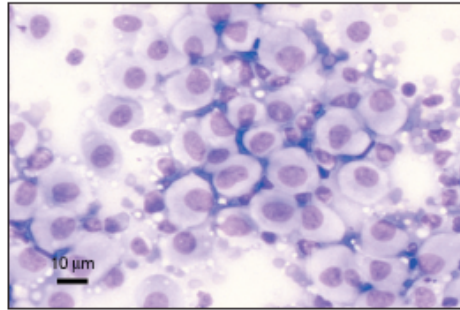


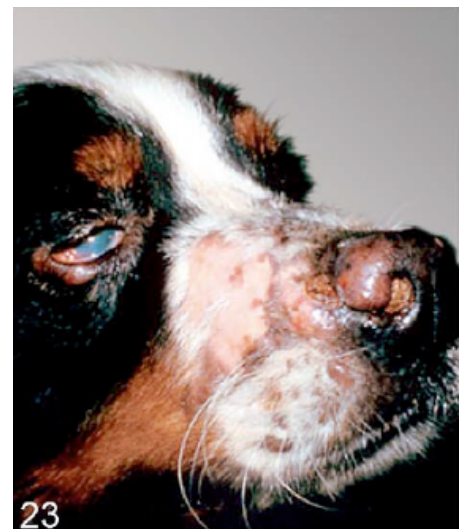
Figure 2. Photomicrograph of a cytology slide from an aspirate of a cutaneous mass on a 2-year-old dog. The mass was diagnosed as cutaneous histiocytoma. Note the pale cytoplasm and round nuclei typical of this cell type. Image courtesy of Dr. Jeff Siminger, Louisiana State University. Bar = 10 μ m.

- solitary lesion in young dogs < 4 years old
- brachycephalics are predisposed (think boxers and bulldogs) and Scottish terriers, Doberman Pinschers and Cocker Spaniels are over represented
- commonly on head or pinna but can occur anywhere
- benign
- no treatment necessary although surgery can be considered in older dogs or when lesions do not regress over long periods
 - usually undergo spontaneous regression in 1-2 months
 - infiltration of mature lymphocytes
- excellent prognosis
 - very rarely multiple lesions or metastasis to a LN
- diagnosis
 - cytopathologic examination
 - histopathologic examination with IHC for definitive
 - identical to canine epidermal Langerhans cell
 - CD1a, CD1b, CD1c, MHC Class II, CD11c, E-cadherin on snap frozen sections
 - E-cadherin can be performed on formalin fixed paraffin sections as well (E-cadherin is unique to Langerhans cells, so specifically identifies canine histiocytoma as a localized epidermal Langerhans cell tumor)

2- Canine Reactive Histiocytoses

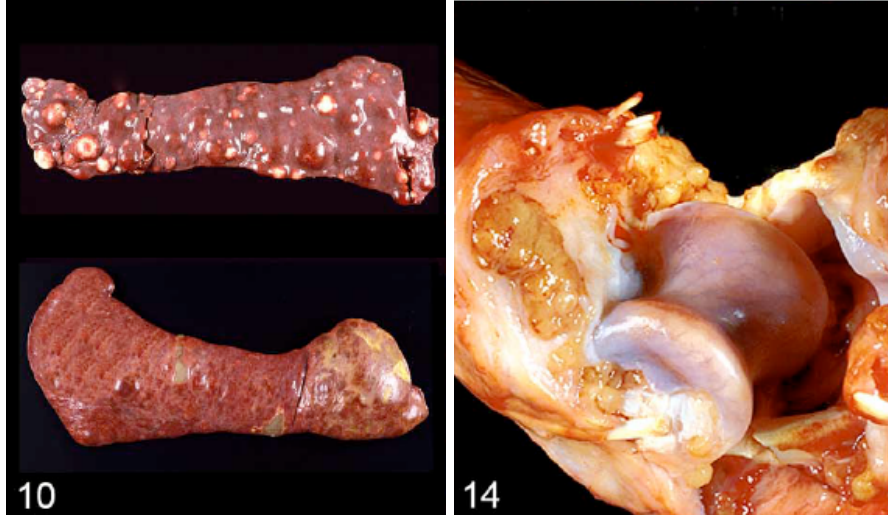
(A Review of Histiocytic Diseases of Dogs and Cats. P.F. Moore. Veterinary Pathology 2014, 51(1) 167-184)

- skin and draining LN (CH, common) OR skin and extracutaneous sites (SH, rare)
 - cutaneous: multiple cutaneous and subcutaneous nodules up to 4 cm in diameter (solitary lesions uncommon). Overlying skin ulceration common.
 - no clear breed disposition
 - systemic: Bernese, Rotties, Labs, Bassets, Irish Wolfhounds (familial)
 - multiple cutaneous nodules over entire body
 - skin, ocular and nasal mucosa, scrotum, peripheral lymph nodes often affected
 - at necropsy: lung, liver, bone marrow, spleen, peripheral/visceral LNs, kidneys, testes, orbital tissues, nasal mucosa, etc
 - young to middle age dogs
 - CS include anorexia, weight loss, stertorous respiration, conjunctivitis chemosis etc
 - ulceration of overlying skin common
 - remission and relapse especially early in disease course
- Morphologic features: SH and CH identical
 - deep dermis and subcutis
 - discrete perivascular lesions affecting mid dermis coalesce in deep dermis and subcutis
 - bottom heavy topography
 - histiocytes and lymphocytes invade vessel walls leading to vasculat compromise and infarction or surrounding tissues > ulceration
- Immunophenotypic features: SH and CH identical
 - DCs markers CD1a, CD11c, CD18, MHC II
 - Histiocytes CD4, CD90, LACK expression of E-cadherin (inverse of phenotype in cutaneous histiocytoma)
- Bernese Mountain Dogs
 - same families as histiocytic sarcomas however progression of SH to HS has not been documented.
- immune dysregulation suspected
 - lesions are thought to be antigen driven but no etiologic agent or antigen has been discovered
 - lesions dominated by activated dermal interstitial DCs and T cells (us CD8+), which frequently infiltrate the walls of dermal vessels creating a lymphohistiocytic vasculitis
 - T cells do not help with regression but rather may encourage proliferation o fDC via GM-CSF and TNF-alpha



- lesions radiate and coalesce to form masses especially in deep dermis and panniculus
- spontaneous remission and relapses
- tx is immunosuppressive or immunomodulatory drugs (prednisolone, cyclosporine A, leflunomide, tetracycline/niacinimide)
 - because of waxing and waning nature spontaneous resolution without therapy occurs

3- Histiocytic sarcoma complex (localized and disseminated)



- malignant diseases characterized by infiltration of neoplastic histiocytes
- middle aged Bernese Mountain Dogs, often with familial association, as well as Rottweilers, flat coated retrievers and golden retrievers
- localized
 - primary lesion involving skin and subcutis or extremities
 - periarticular tissues surrounding large appendicular joints, spleen, LN, lung, or bone marrow
 - present for soft tissue swelling and/or lameness
 - locally invasive
 - local metastasis to draining LNs common
 - treatment
 - surgical excision or amputation of limb
 - excise draining LNs at time of surgery or treat with radiation post op
 - curative intent radiation therapy (incompletely or non resectable tumors) some efficacy
 - better prognosis than disseminated
 - consider systemic chemotherapy due to risk of aggressive biologic behavior
 - may just represent an earlier stage of disseminated histiocytic sarcoma
 - diagnosis with CD 18 antibody on histopath

- disseminated
 - clinical signs
 - anorexia, lethargy, weight loss
 - dyspnea due to pulmonary involvement
 - lameness due to large extremity mass
 - ataxia and paraparesis due to intervertebral lesions
 - lesion location
 - anywhere
 - often spleen, lungs and bone marrow
 - on necropsy usually in most organs
 - difficult to differentiate from malignant histiocytosis, which also effects Bernese Mountain Dogs
 - disseminated lesions that simultaneously arise in multiple organs (skin, spleen, liver, LN, BM)
 - both condition are called disseminated histiocytic sarcoma
 - treatment
 - complete staging prior to therapy (for both forms)
 - minimum database for staging: CBC, CHEM, UA, chest rads, abd rads/ultrasound and bone marrow biopsy
 - aspirates of regional LNs
 - prognosis for disseminated is poor even with aggressive therapy >> systemic chemotherapy
 - median survival 3-6 month range
 - lomustine, doxorubicin, paclitaxel
 - diagnosis
 - histopath: poorly demarcated, effacement of normal tissue architecture,
 - large vacuolated round cells and plump mesenchymal cells

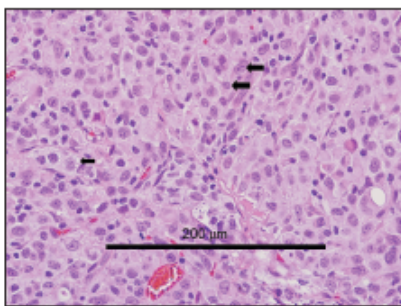


Figure 3. Photomicrograph of a biopsy from a mass surrounding the right elbow of a 9-year-old rottweiler. Note the presence of vacuolated round cells (small arrow) as well as mesenchymal cells, along with a high degree of anisokaryosis (two large arrows). The tumor was diagnosed as a histiocytic sarcoma. Image courtesy of Dr. Scott Reed, Louisiana State University. Bar = 200 μ m.

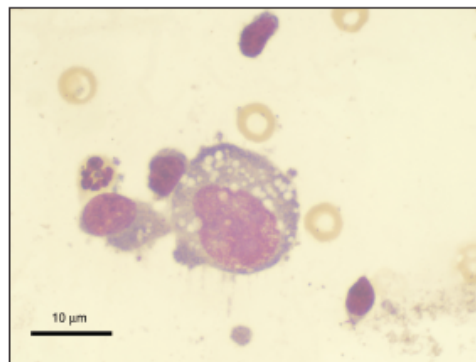


Figure 4. Photomicrograph of the aspirate from the rottweiler in Figure 2. The photo shows a large round histiocytic cell with the typical vacuolated appearance. Image courtesy of Dr. Jeff Siringer, Louisiana State University. Bar = 10 μ m.

- bizarre multi-nucleated giant cells are also characteristic
- anisokaryosis and anisocytosis with high mitotic rate
- phagocytosis of neutrophils and RBCs

- inflammatory infiltrate may be seen
- IHC
 - no known means of differentiating between localized and disseminated forms
 - myeloid dendritic APC likely from dendritic and not macrophage lineage (CD18, CD1abc, CD11c, MHCII)
 - lack expression of E-cadherin (not Langerhans origin)
 - no Thy-1 or CD-4 expression (inconsistent with reactive histiocytosis)
 - no CD79a or CD3 (not lymphoid origin)
 - no CD11b (not macrophage origin)
- immunophenotyping + histopathologic examination
 - distinguish from lymphomas, poorly differentiated MCT, malignant fibrous histiocytomas

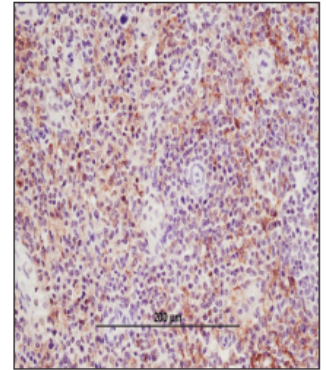


Figure 5. Photomicrograph of splenic tissue exhibiting diffuse CD18 staining by immunohistochemistry. The CD18 positive cells are identified by their golden-brown staining pattern. CD18 staining is performed on formalin-fixed tissue and although it is a broad leukocyte marker, staining is prominent in histiocytic tumors. Image courtesy of Dr. Tim Morgan, Louisiana State University. Bar – 200 μm.

4- Malignant fibrous histiocytomas

- soft tissue sarcoma that is often confused with histiocytic sarcoma
- may not even be a true identity but rather a group of undifferentiated pleiomorphic sarcomas. Many need to be reclassified upon review to various sarcomas.
- presentation
 - most often limb or trunk
 - also spleen and other organs
 - middle age to older
 - Rottweilers and golden retrievers
 - locally invasive with a low to moderate risk of metastasis (~15%)
- therapy
 - complete surgical resection
 - definitive radiation therapy after surgery for residual disease
 - questionable recommendation for chemotherapy unless high grade tumor on histopathology
- prognosis
 - favorable (75% 5 year survival rate)
- studies have been done with conflicting results however no IHC was performed so it is possible that tumors in those studies would need to be reclassified.
- morphologically
 - mesenchymal cells; fibroblastic in appearance and arranges in storiform pattern
 - scattered multi-nucleated giant cells
- no definitive IHC staining pattern

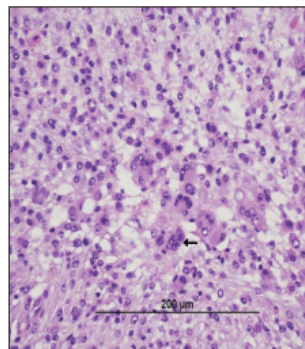


Figure 6. Histopathology of a malignant fibrous histiocytoma removed from the left lateral thorax of a 6-year-old rottweiler. A large population of mesenchymal cells was identified. Occasional multinucleated giant cells were noted (arrow). Image courtesy of Dr. Tim Morgan, Louisiana State University. Bar – 200 μm.

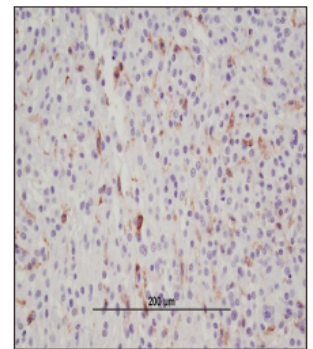


Figure 7. Immunohistochemical staining of tissue from the same dog identified in Figure 5 with an MFH. Occasional CD18 positive cells can be identified within the tissue; in this tumor the CD18-positive cells are consistent with non-malignant macrophages infiltrating tumor tissue. Image courtesy of Dr. Tim Morgan, Louisiana State University. Bar – 200 μm.

Questions:

1. In terms of histiocytic neoplasia, A Basset presenting with multiple cutaneous nodules of waxing and waning incidence with nasal mucosa and scrotum affected would be most consistent with which of the following:
 - a. canine cutaneous histiocytoma
 - b. Cutaneous canine reactive histiocytosis
 - c. Systemic canine reactive histiocytosis
 - d. Histiocytic sarcoma
2. The most appropriate treatment for the likely disease affecting a 2 year old boxer presenting with a solitary lesion on his pinna would be:
 - a. surgical excision
 - b. radiation
 - c. surgery + radiation
 - d. no treatment
3. A 5 year old Bernese Mountain Dog presents for lameness in the left fore and on physical exam a mass is palpated in the axillary region. Which of the following markers would you be most likely to detect with IHC?
 - a. CD18
 - b. E-cadherin
 - c. CD11b
 - d. CD4
4. True or False: IHC can differentiate between localized and disseminated forms of Histiocytic Sarcoma Complex.

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