THE GOOD, THE BAD, AND THE UGLY: A REVIEW OF THE UNUSUAL AND DIVERSE GROUP OF HISTIOCYTIC DISEASES

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Sponsor

Objectives

Review histiocytes including cellular markers

Review histiocytic diseases in dogs

Evaluate different stains used to diagnose histiocytic diseases

Identify common histiocytic diseases in cats

Overview of Histiocytes

Histiocyte

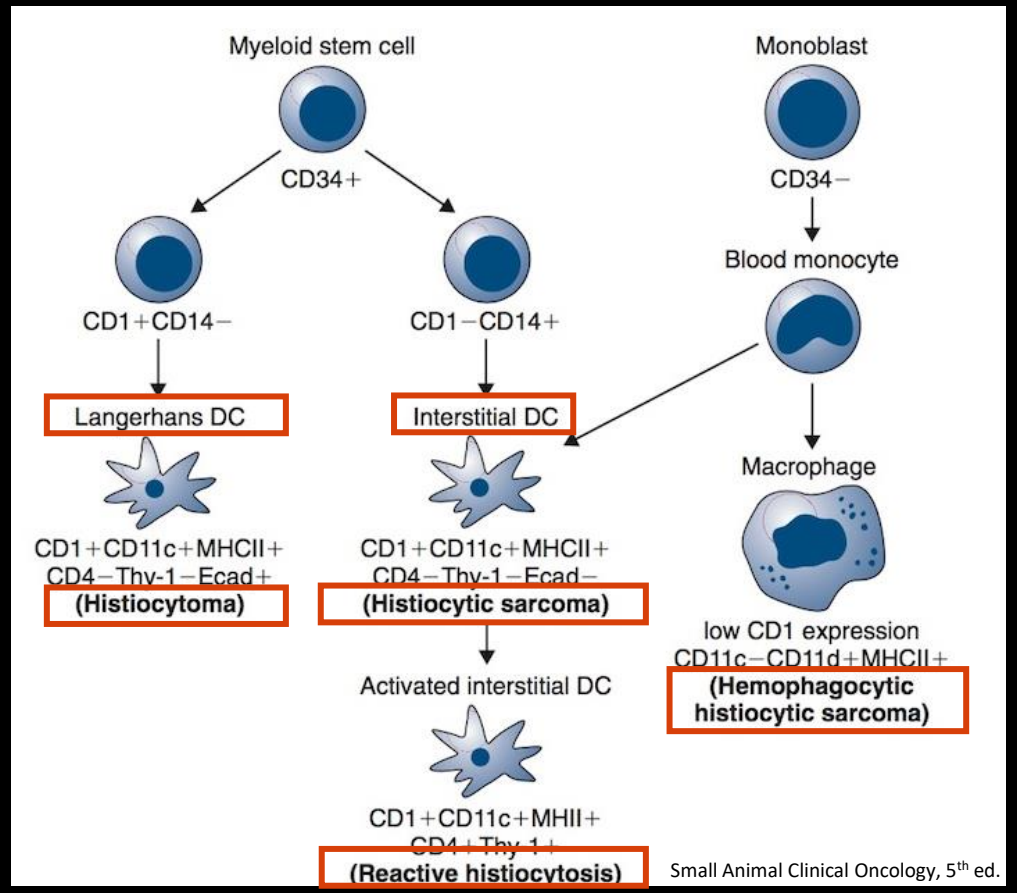
- General term for: Dendritic cell (DC), Monocyte, Macrophage
- Function: phagocytosis, antigen presentation, interaction with lymphocytes

3 types of dendritic cells

- Langerhans
- Interstitial DC
- Myeloid

Most histiocytic disease involve:

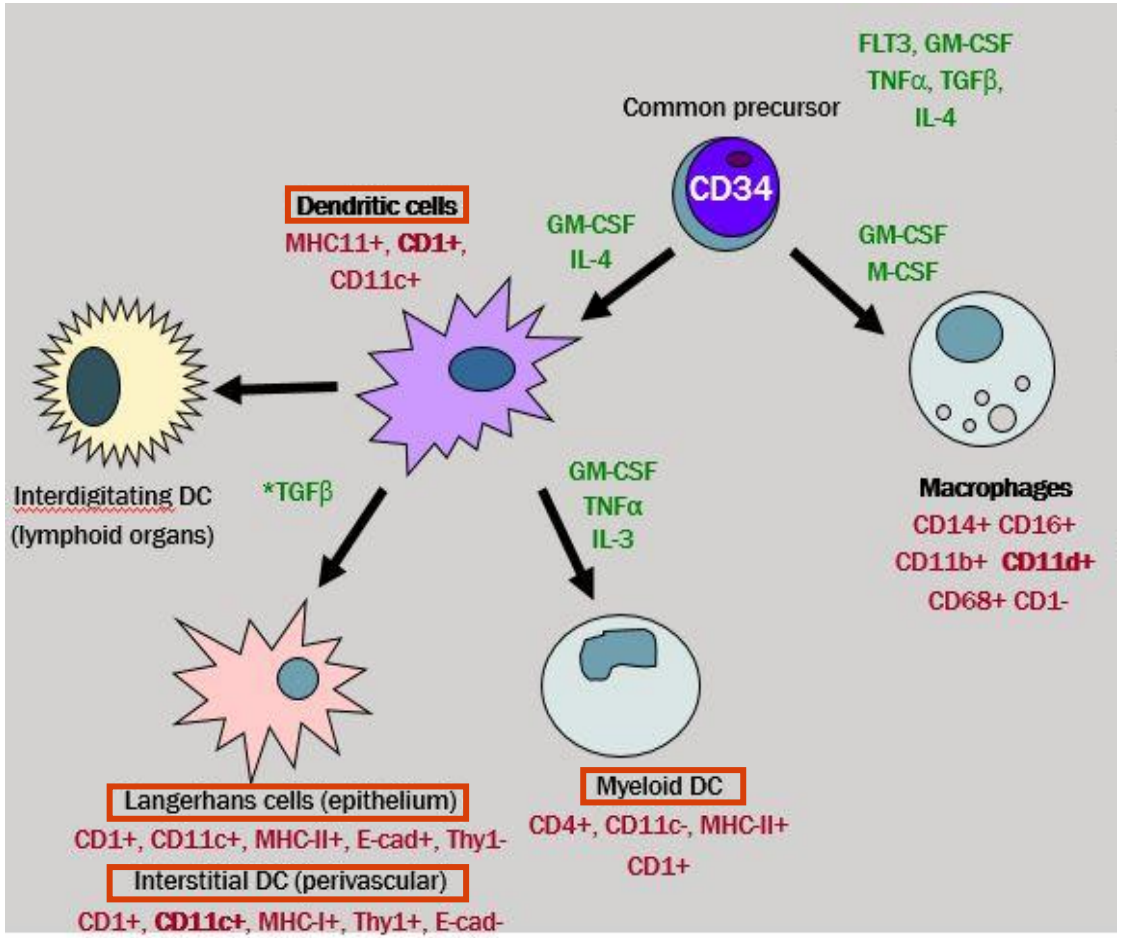
- Langerhans or interstitial DC
- Hemophagocytic HS exception- macrophage in origin



Small Animal Clinical Oncology, 5th ed.

Dendritic Cell Phenotypes

- Antigen Presenting Cells (APCs)
- Langerhans
  - Located within epithelia of the skin, alimentary, respiratory and reproductive tracts
  - E-cadherin attaches cells to keratinocytes
- Interstitial
  - Perivascular locations in many organs except the brain
  - Migrate to many tissues including dermis, but not epidermis
- Myeloid
  - Immature DC migrate through vasculature to lymphoid organs
  - Differ from other DC which require activation to migrate to lymph nodes

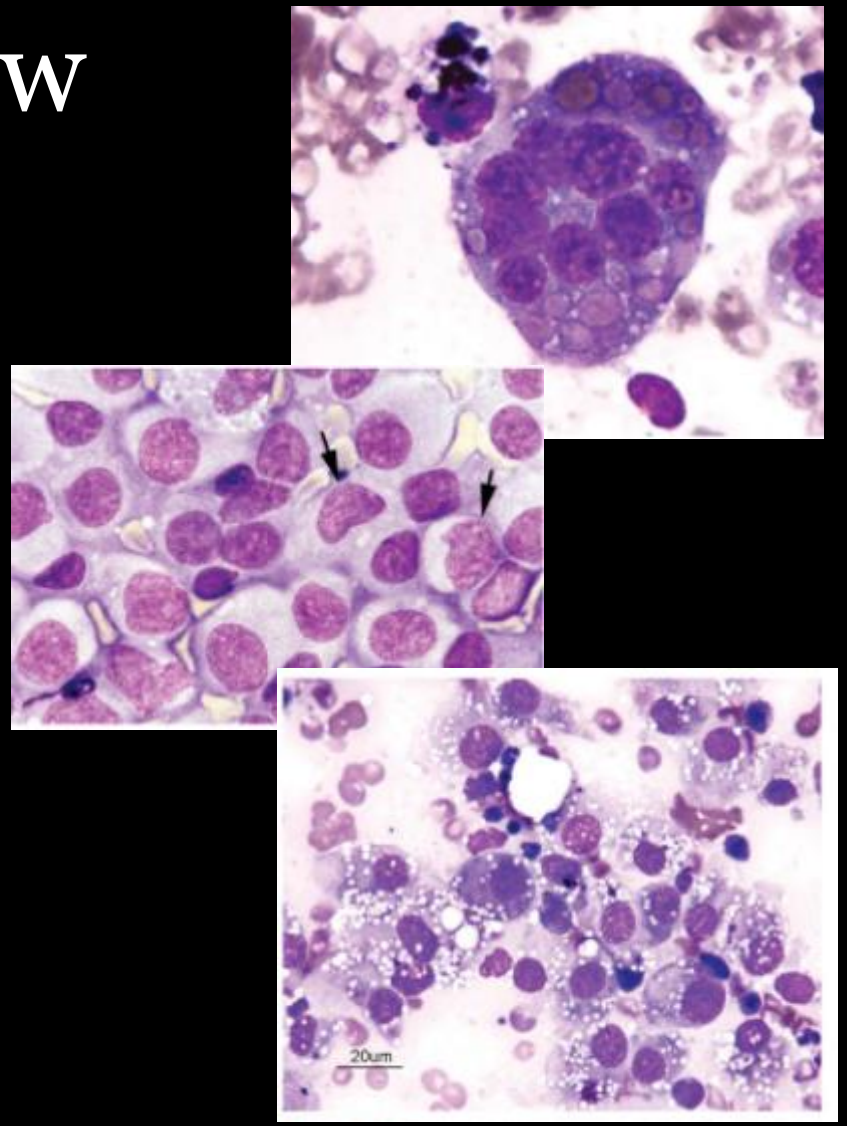


Green text – cytokines and growth factors

Red text – cell markers/phenotype

Histiocytic Diseases Overview

Wide Range in Clinical Presentation and Biologic Behavior	• Complex set of diseases within this group
Difficult to Diagnose with Cytology/Histology	• Wide variation in appearance • May have benign, normal looking cells
Cellular Features Common to Histiocytes/Histiocytic Diseases	• Large, round to oval cells- discrete round cells • Eccentric, oval to indented nuclei with lacey chromatin, can be multinucleated
Additional Staining Often Required	• Immunocytochemistry- nonspecific esterase activity (NSEA) • Immunohistochemistry- several stains available



Cowell RL et al. Diagnostic Cytology and Hematology, 3rd ed.

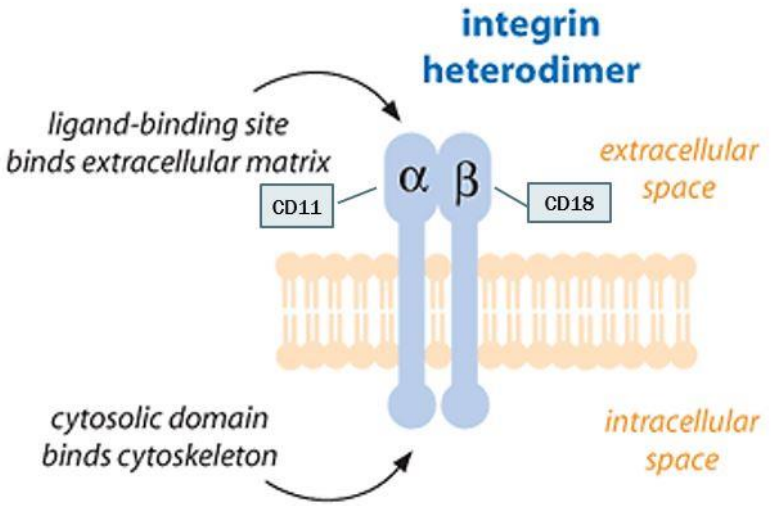
Cellular Markers

Dendritic Cells

- Express CD1a and MHC Class I and Class II
- Help present peptides, lipids and glycolipids to T cells

CD11 & CD18

- CD18 common stain used to help diagnose histiocytic disease
- Adhesion molecule requires:
  - 1 of 4 alpha subunits (CD11a-d)
  - Single beta subunit (CD18)
- Expressed by ALL LEUKOCYTES
  - Should use other stains to rule out lymphoma (CD3, CD79a)



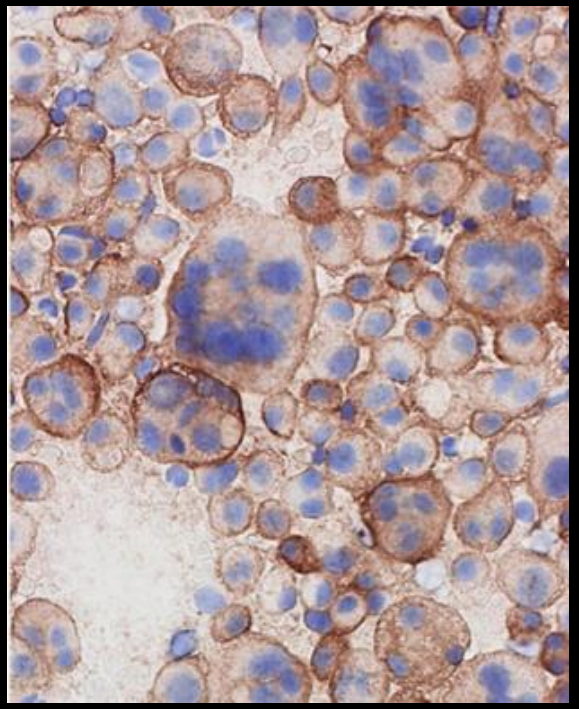
Cellular Markers

CD204
- Expressed by neoplastic histiocytes and normal, resident infiltrating macrophages
- Sensitive and specific for histiocytic sarcoma

Iba-1
- Does not differentiate between macrophages and dendritic APCs
- Histiocytomas, histiocytic sarcoma, feline progressive histiocytosis

E-Cadherin
- Cell-to-cell adhesion, expressed by epithelial cells and
- Found in histiocytomas
  - Not in regressing histiocytomas

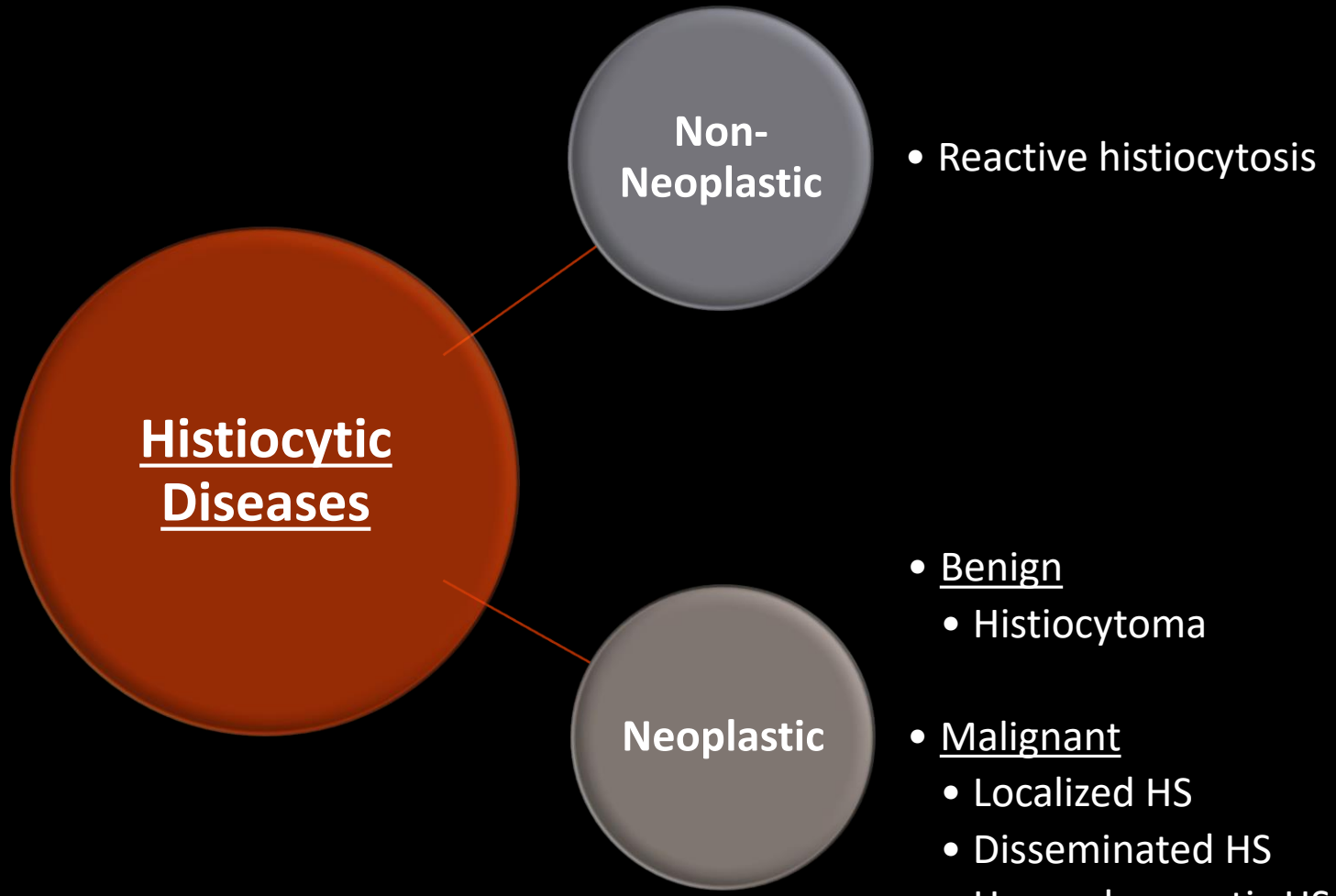
Mum1
- Multiple myeloma oncogene 1
- Plasma cell tumors, histiocytomas



Kato Y, Funato R, Hirata A, et al. Veterinary Clinical Pathology 2014

CANINE HISTIOCYTIC DISEASES

Overview of Histiocytic Diseases- Canine



Misnomer: malignant fibrous histiocytoma- NOT a histiocytic disease!

Reactive Histiocytosis

Overview

- Non-neoplastic process
  - Exact etiology and pathogenesis unknown
- Arise from activated dermal DCs

Clinical Progression

- Spontaneous remissions and relapses have occurred
- Progression to histiocytic sarcoma NOT described

Identified Only in Dogs

- Age ranges: 2-13 years
- Breeds:
  - Originally described in Bernese Mountain Dogs
  - Other large breed dos: Rottweiler, Golden Retriever, Basset Hounds, Irish Wolfhound

Reactive Histiocytosis

Moore PF. Veterinary Pathology 2014

Two Forms

- Cutaneous: more common
  - Multiple haired/alopecic plaques/nodules located on head, neck, extremities or trunk
  - Nasal planum: clown-nose appearance
- Systemic

Clinical Presentation

- Depression, anorexia, weight loss, conjunctivitis
- Hypercalcemia (2/26)
- Anemia, monocytosis, lymphopenia
- Erythrophagia- uncommon

Diagnosis

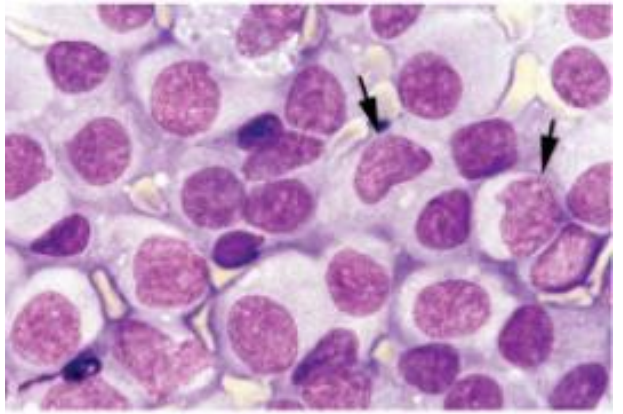
- IHC on fresh, snap-frozen tissue
- CD1+, CD11c+, MHCI+, CD4+ and Thy1+

Treatment

- Immunosuppressive drugs +/- antibiotics

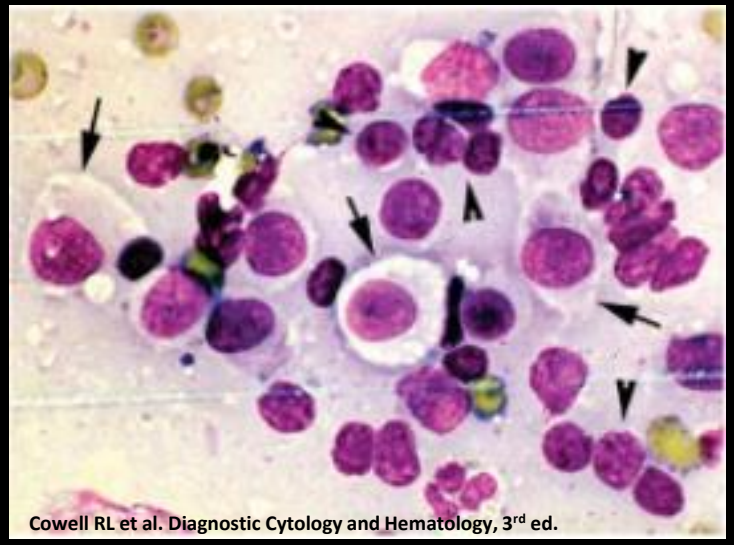
Histiocytoma

- Overview
  - Benign tumor of Langerhans DC in skin
    - CD1a and E-cadherin+
- Lesion Description and Location
  - Often single, cutaneous lesion on young dog (<3yrs)
  - Can occur as multiple tumors (cutaneous LH- next group)
  - Common on cranial half of body
  - Growth often rapid (1-4 weeks)
- Diagnosis
  - History, presentation
  - Cytology
  - Histopathology (IHC rarely needed)



Cowell RL et al. Diagnostic Cytology and Hematology, 3rd ed.

Histiocytoma



Cowell RL et al. Diagnostic Cytology and Hematology, 3rd ed.

Table 1. Signalment and location of primary tumour and metastatic lymph node(s) in dogs with histiocytoma

Case number	Age at diagnosis/ months	Gender	Breed	Tumour location	Metastatic lymph node
1	60	Spayed female	Pug	Carpal pad	Prescapular
2	3·5	Female	Boxer	Head	Mandibular, prescapular
3	2·5	Female	Mixed	Vulva	Inguinal
4	6	Female	Flat-coated retriever	Gingiva	Mandibular
5	24	Neutered male	Boxer	Ear canal	Mandibular, retropharyngeal, prescapular
6	30	Male	Bernese mountain dog	Front paw	Prescapular
7	6	Male	Yorkshire terrier	Lateral thigh	Inguinal
8	3	Female	American pit bull terrier	Stifle	Inguinal

Faller M, Lamm C, Affolter VK et al., J Small Anim Pract 2016

Treatment

- Surgical resection
  - Recurrence and development of new de novo tumors are rare
- Benign neglect
  - Often spontaneously regress within 1-2 months
  - Mediated by mature lymphocyte infiltration, CD8+ cytotoxic T cells, reduced levels of E-cadherin
  - MMP-9 and angiogenesis involved in regression

Metastasis

- VERY RARE
- Case Series from JSAP 2016 reported 8 cases with LN metastasis
  - Most treated with complete surgical removal but some diagnosed via biopsy
  - Most had prolonged survival with no recurrence or experienced complete remission of tumor and metastasis

Prognosis

- Excellent

Cutaneous Langerhans Cell Histiocytosis

Overview

- Numerous cutaneous histiocytoma lesions
  - Can have hundreds of lesions (nodules->masses)
  - Lesions at mucocutaneous lesions or oral cavity can occur
- Shar Pei Dogs overrepresented
  - 20% of cases

Disease Presentation/Progression

- Delayed regression, can persist for up to 10 months
- Rarely involve internal organs
  - Prognosis worse with LN involvement

Treatment

- Cyclosporine
- CCNU- responses not durable
- Griseofluvin- immune modulating antibiotic

Histiocytic Sarcoma

Overview

- Malignant proliferation of histiocytic cells
  - Interstitial dendritic cells or macrophages (hemophagocytic)
- May be localized or disseminated

Signalment

- Age: middle-aged to older
  - Reported as young as 3 years of age
- No sex predilection
  - Slight male predilection in one study of Bernese Mountain Dogs
- Can occur in any breed
  - Common breeds: Bernese Mountain Dogs, Flat-Coated Retrievers, Rottweilers, Labrador Retrievers, Golden Retrievers, Miniature Schnauzers, Corgis

Histiocytic Sarcoma

Clinical Signs

Signs vary depending on site of involvement

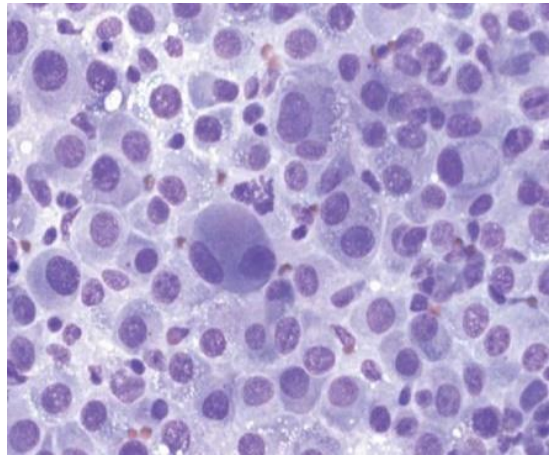
Non-specific systemic signs

- Lethargy, poor appetite, weight loss

Diagnosis

Cytology or histology

Special stains (CD18, CD204, Iba-1)



Histiocytic Sarcoma

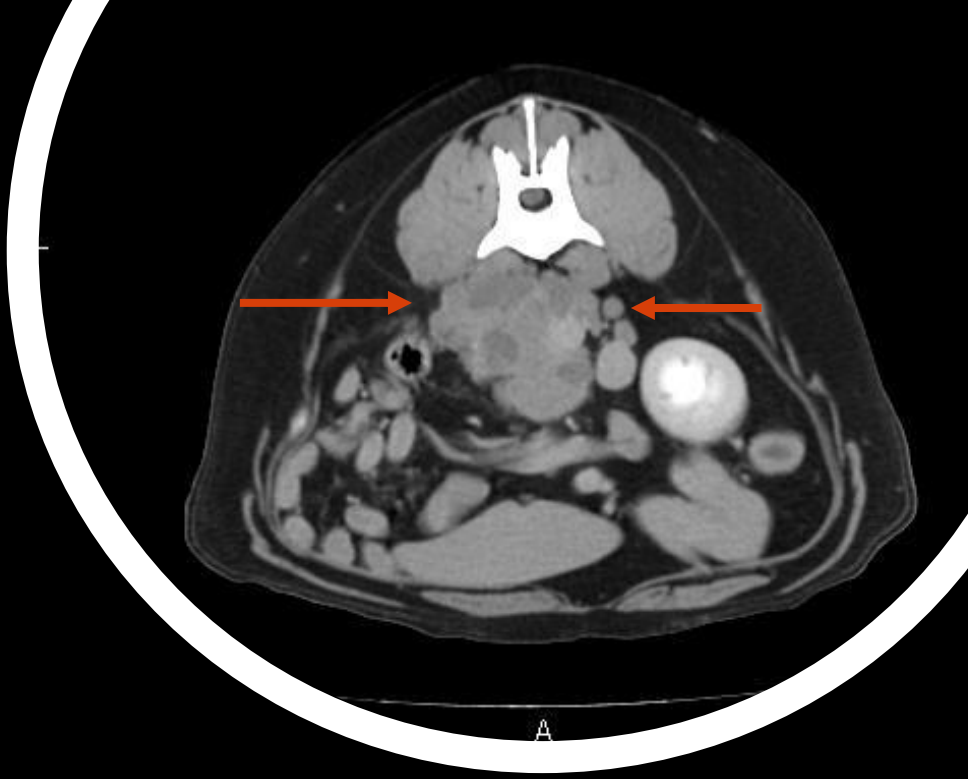
Staging

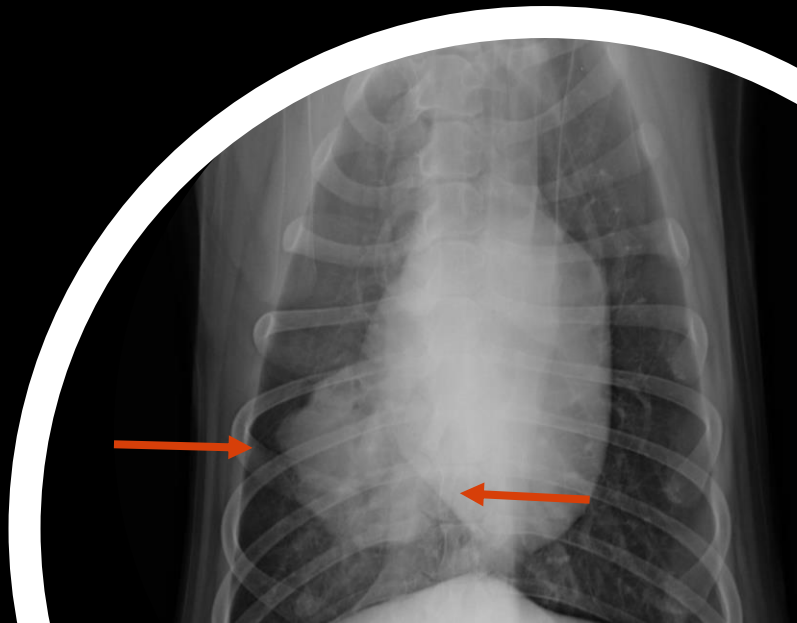
Lab work
- CBC
- CHEM
- Ferritin

Imaging of the thorax and abdomen

LN aspirates

+/- BM aspirates





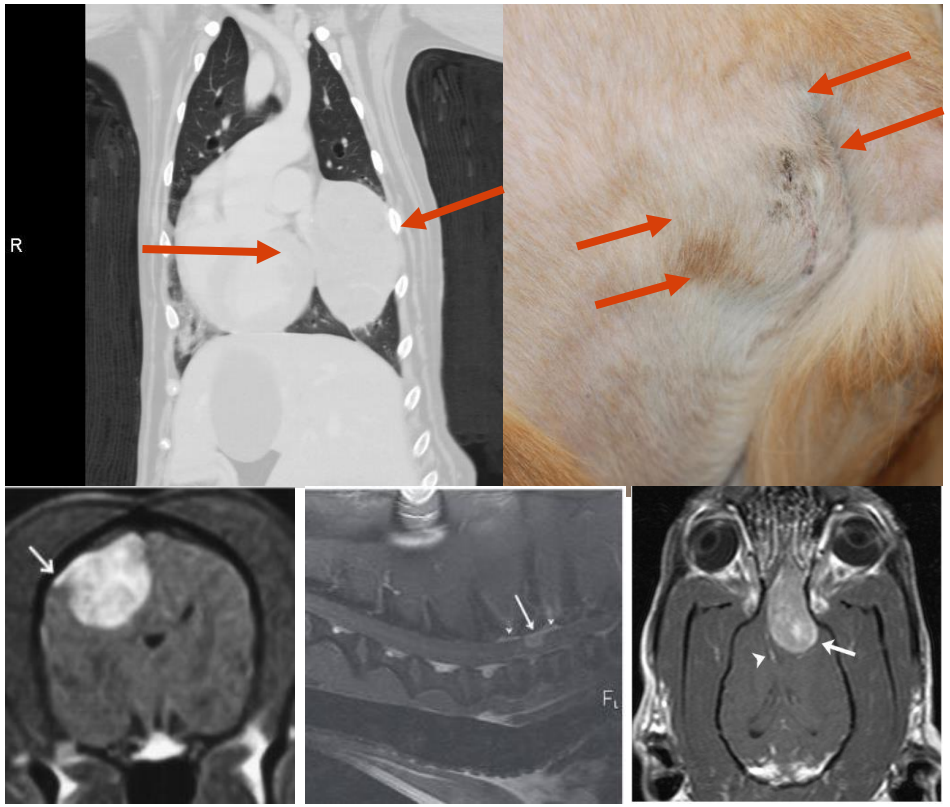
Histiocytic Sarcoma- Localized

Overview

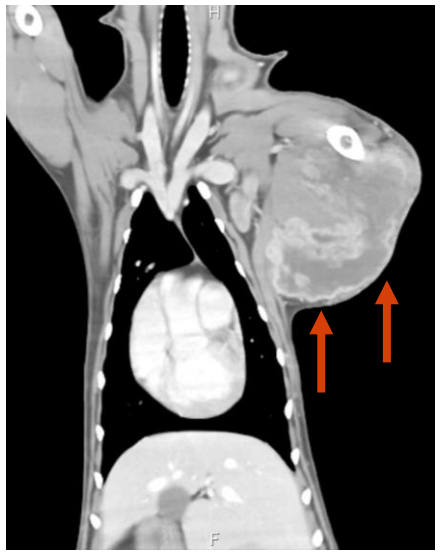
- Rapidly growing, locally invasive, affect a single site

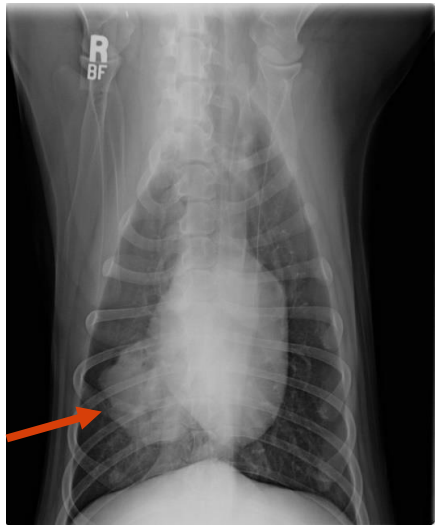
Sites

- Spleen
- Lungs
- Liver
- Stomach
- Skin/SQ
- Bone, joint and/or periarticular (PAHS)
- CNS



Tamura S, Tamura Y, Nakamoto Y, et al. Vet Radiology Ultrasound 2009





Histiocytic Sarcoma - Localized

Metastatic Rates

- PAHS- 60-90%
- Skin/SQ- 38-60%

Treatment

- Local therapy + adjuvant chemotherapy
- Long-term survival reported by Skorupski et al. VCO 2009
  - 16 dogs- wide variety of sites
  - CCNU chemotherapy
  - DFI 243 days
  - MST 568 dogs
- Survival times for surgery alone in some studies is around 180 days

Histiocytic Sarcoma- PAHS

Overview

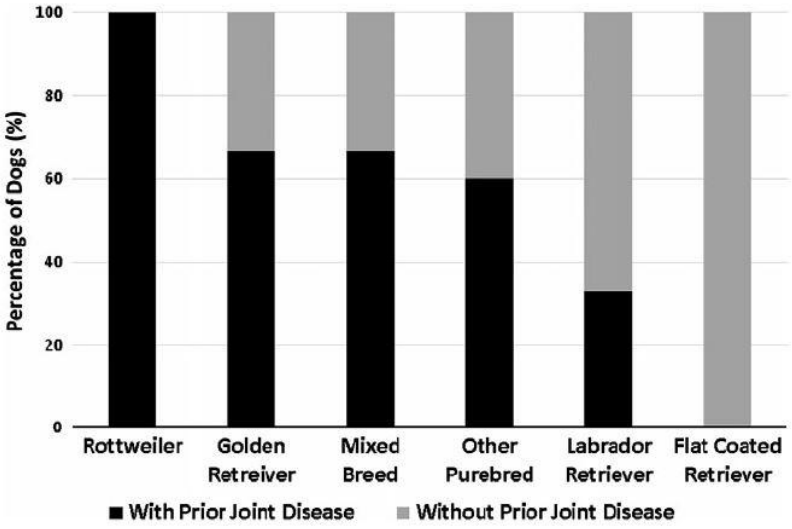
- Most common synovial tumor in dogs (51%)
- Rottweilers overrepresented
- Prior joint disease increases risk
  - In one study of Bernese Mount Dogs- anti-inflammatories decreased risk

Treatment

- Local therapy
  - Wide surgical resection (amputation)
  - Radiation- recent study had no difference in TTP or OST compared to amputation
- Chemotherapy

Prognosis

- Metastasis at diagnosis significant prognostic factor
  - MST without metastasis- 980 days
  - MST with metastasis- 253 days



Manor EK, Craig LE, Sun X, Cannon CM. Vet Comp Oncol 2017

Histiocytic Sarcoma- Pulmonary

Overview

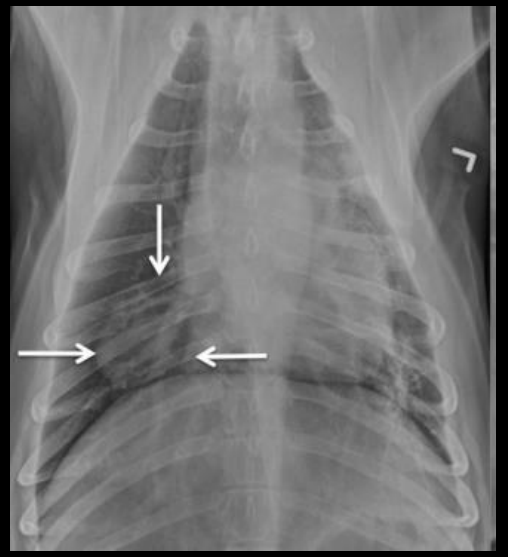
- Commonly found in L cranial and R middle lung lobes
- HS often larger than other primary lung tumors on imaging
- Intrathoracic lymphadenopathy 82-87%
- Miniature Schnauzers and Corgis

Treatment

- Surgery + Adjuvant chemotherapy
  - Longer MST likely than those treated with surgery alone
    - Sx + chemo- 374 days
    - Sx alone- 131 days

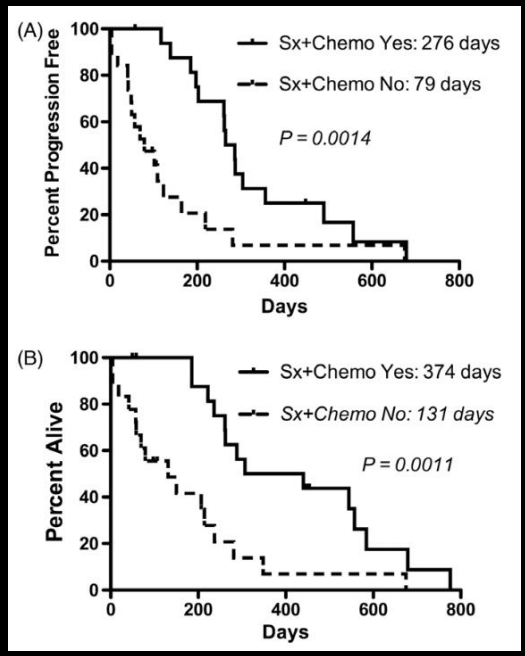
Prognosis

- Unclear if contribution of chemotherapy is significant with low numbers in study
- One study looked at gender, age, single/multiple nodules, LN involvement, surgical resection, chemo for prognosis- none reached significance



Barrett LE, Pollard RE, Zwingenberger A, et al. Vet Rad Ultra 2014

Marlowe KW, Robat CS, Clarke DM, et al. Vet Comp Oncol 2018



Histiocytic Sarcoma- Splenic

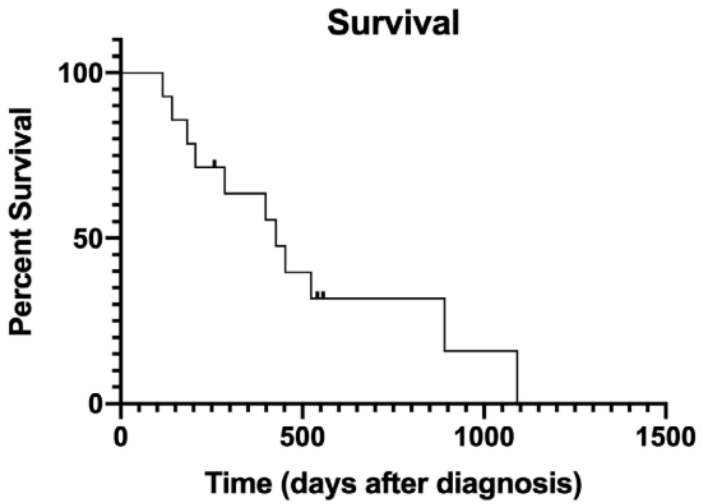


FIGURE 1 Kaplan–Meier survival curve estimating overall survival in 14 dogs that underwent surgical removal of splenic histiocytic sarcoma. Three dogs were censored from survival analysis. Day 0 designates the day of surgery

Latifi M, Tuohy JL, Coutermarsh-Ott SL. et al. J Vet Intern Med 2020

Overview

- Few studies have looked at localized splenic histiocytic sarcoma alone

Latifi M. et al. JVIM 2020

- 14 dogs
- Treatment
  - 12 had surgery + chemotherapy
  - 2 had surgery alone
- 35% of dogs were suspected or confirmed to have metastatic disease
- 11 died because of tumor
- MST 427 days

Histiocytic Sarcoma- Disseminated

Disseminated Histiocytic Sarcoma

- Aggressive, multiple sites of involvement
- AKA- malignant histiocytosis

Hemophagocytic Histiocytic Sarcoma

- Arise from macrophages in spleen or bone marrow
- Often very sick
- Carries worst prognosis of all forms

Hemophagocytic Syndrome

- Anemia, thrombocytopenia, hypocholesterolemia, hypoalbuminemia
- Confused with IMHA- regenerative anemia, hyperbilirubinemia without jaundice

Moore PF. Veterinary Pathology 2014

Histiocytic Sarcoma- Disseminated

Treatment

- Systemic therapy only (chemotherapy)
  - CCNU- response rate of 46%
  - Doxorubicin – response rate of 58% when combined with CCNU
  - Others- dasatinib, dacarbazine, epirubicin, vinorelbine, bisphosphonates
- Surgery often not recommended unless palliative

Prognosis

- Poor overall
  - No treatment- MST of 2-57 days
  - Chemotherapy- MST of 102-185 days
- Prognostic factors
  - Associated with increased risk of death: palliative treatment, disseminated form vs. localized, LN metastasis in localized forms, concurrent use of corticosteroids

Histiocytic Sarcoma- Summary

Disease	Anatomic Predilections	Blood work Abnormalities	Treatment and Outcome
Localized HS	• Periarticular • Skin/SQ • Lung • Spleen • Other less common	• Often normal	• High metastatic rate • 3–4-month survival if untreated • 6-12+ month survival with local and systemic treatment
Disseminated HS	• Multiple sites or organs • Spleen, liver, lung, lymph nodes, kidneys	• Variable	• 1–2-month survival if untreated • 5-6 months survival if respond to chemotherapy
Hemophagocytic HS	• Spleen +/- liver • Bone marrow, lung Lymph node	• Anemia (regenerative) • Thrombocytopenia • Hypoalbuminemia • Hypocholesterolemia	• Poor response to chemotherapy • 1–2-month survival

FELINE HISTIOCYTIC DISEASES

Feline Histiocytic Diseases

Histiocytic Neoplasms are Rare in Cats

Subtypes Identified:

- Histiocytic Sarcoma
- Hemophagocytic histiocytic sarcoma
- Feline Progressive Histiocytosis
- Pulmonary Langerhans Cell Histiocytosis

Feline Histiocytic Sarcoma

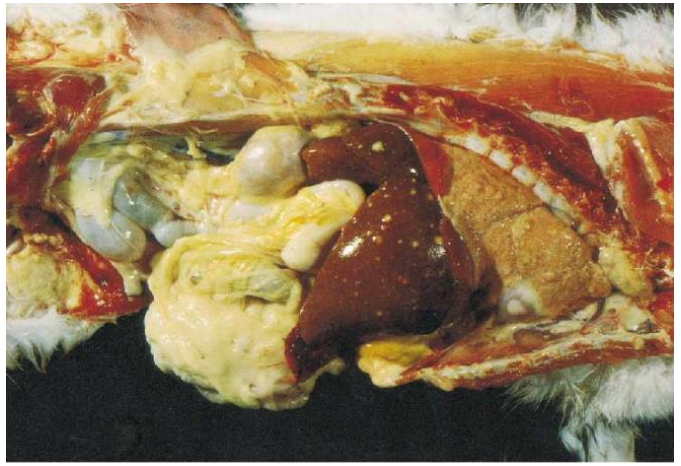
Histiocytic Sarcoma & Hemophagocytic Histiocytic Sarcoma

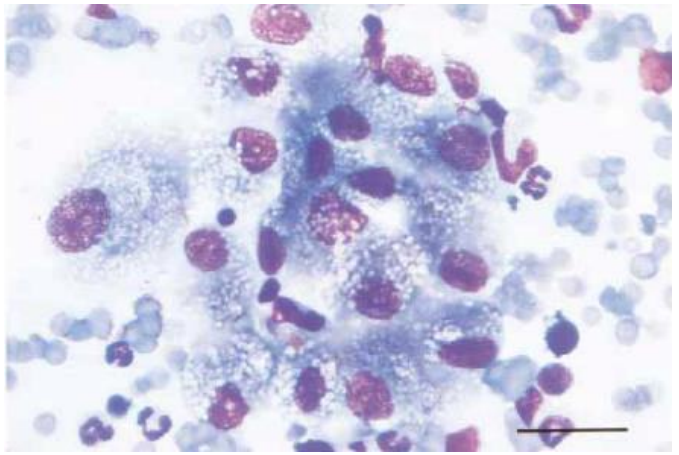
Presentation:

- Usually present with non-specific signs- lethargy, inappetence, weight loss
- Disseminated disease is common
- Nonregenerative anemia and thrombocytopenia common
- Only around 10 cases reported in the literature
  - 8/10 cats negative for FeLV and FIV

Treatment:

- Effective treatment is not known
- Lomustine has been used
- Short survivals reported (weeks-months)





Kraje AC, Patton CS, Edwards DF. JVIM 2001.

Feline Progressive Histiocytosis

Coste M, Prata D, Castiglioni V, et al. J of Vet Diagn Invest 2019.

Overview:

- Proliferation of interstitial dendritic cells
- Most common histiocytic disease in cats
- Often compared to canine reactive histiocytosis
- Immune-mediated etiology is hypothesized

Presentation:

- Middle aged to older cats (7-17 years)
- Nodules and plaques spread diffusely
  - Location: head, extremities, trunk
  - Can wax and wane, spontaneous remission not reported
- Often have disseminated disease to internal organs
  - Liver, spleen, bone marrow

Feline Progressive Histiocytosis

Treatment

- Chemotherapy, immunosuppressive agents
  - Lomustine, TKIs
- Surgery not successful long-term
  - One study of 19 cats- recurrence in 14 with DFI of 175 days

Prognosis

- Poor long term
- MST in one study was 96 days (9/19)
  - Follow-up on other 10 cats was 41-1449 days
- Ki67 may be prognostic in one stud of 26 cats

Moore PF. Veterinary Pathology 2014

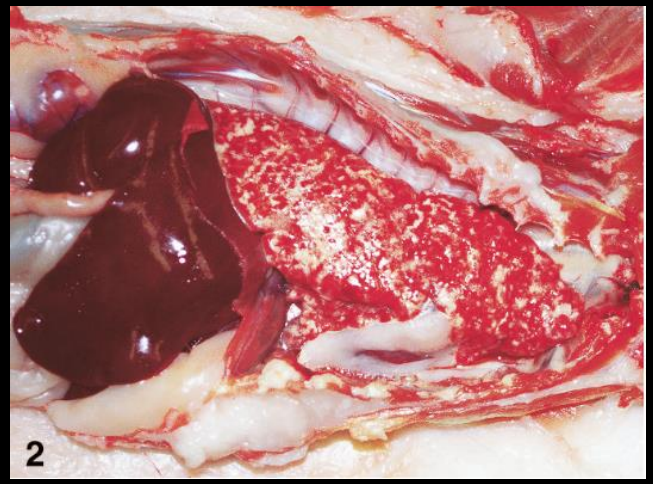
Feline Pulmonary Langerhans Cell Histiocytosis

Overview

- 11 cases reported to date
  - All diagnosed at necropsy
- Older cats (10-15 years)

Presentation

- Progressive respiratory failure
- Extensive obliteration of pulmonary parenchyma by infiltrating Langerhans cells



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Questions