Canine Histiocytic Disorders

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Canine Histiocytes

- Cells derived from CD34+ stem cells and blood monocytes
- Macrophages
- Dendritic cells (DC)
  - Potent antigen presenting cells (APCs)
  - Langerhans DCs in the epithelium
  - Interstitial DCs in perivascular locations
  - Interdigitating DCs in T cell rich regions of the lymphoid tissues
    - Migratory DC
    - Resident DC
Canine Histiocytic disorders

- Neoplastic
  - Histiocytoma
  - Histiocytic Sarcoma
    - Localized
    - Disseminated
    - Hemophagocytic
- Reactive
  - Cutaneous Histiocytosis
  - Systemic Histiocytosis
Canine Histiocytic Disorders

Myeloid stem cell

CD34+

CD1+CD14−
Langerhans DC
CD1+CD11c+MHCII+CD4−Thy-1−Ecad+ (Histiocytoma)

CD1+CD14−
Interstitial DC
CD1−CD11c+MHCII+CD4−Thy-1−Ecad− (Histiocytic sarcoma)

Activated interstitial DC
CD1+CD11c+MHCII+CD4+Thy-1+ (Reactive histiocytosis)

Monoblast
CD34−
Blood monocyte

Macrophage
low CD1 expression
CD11c−CD11d+MHCII+
(Hemophagocytic histiocytic sarcoma)
Histiocytoma

- Primarily young dogs
- Purebred dogs
- Solitary lesion
- Head or pinna
- Growth can be rapid
- Rare Incidence
  - Cutaneous Langerhans Cell Histiocytosis
  - Recurrence after removal
  - Metastasis
- Diagnosis: cytology
Canine Histiocytoma
Canine Histiocytoma Treatment

- No treatment typically required
- Spontaneous regression within 1-2 months
- Mediated by infiltrating cytotoxic T cells
- Histologically could be mistaken for T cell lymphoma
- Immunosuppressive therapy not recommended
- Surgery may be considered if a lesion is not regressing over long periods of time or cytology is inconclusive
Cutaneous Histiocytosis

- Younger dogs, no specific breeds
- Lesions limited to the skin and subcutis
- Multifocal lesions, may wax and wane
- Diagnosis: histopathology
- Histology: histiocytes are located in the perivascular region, T cell infiltration
- Often follows a benign course
- Treatment: immunosuppressive therapy
  - Prednisone alone is effective in many cases
  - Cyclosporine A, azathioprine, tetracycline/niacinamide
- Prognosis: excellent
Systemic Histiocytosis

- First described in BMD in 1984
- Familial associations
- Young to middle-aged dogs
- Same underlying immune dysregulation as cutaneous histiocytosis
- Skin, lymph nodes, nasal mucosa
- Clinical signs: anorexia, weight loss, upper airway signs
- Lesions can wax and wane
- Treatment: cyclosporine A or leflunomide
- Prognosis: good
Localized and Disseminated HS

- Interstitial DCs present in almost all tissues
- First recognized in BMD as a familial disease in 1986
- Other breeds: Golden Retrievers, Flat-Coated Retrievers, and Rottweilers
- Defect in tumor suppressor genes
- Localized: articular/periarticular, spleen, lung, skin
- Disseminated
- Clinical signs:
  - Lethargy, anorexia, weight loss
  - Specific signs related to the tumor site in localized form
Localized and Disseminated HS

- **Staging**
  - Abdominal u/s
  - Thoracic radiographs
  - Local lymph node cytology

- **Diagnosis:**
  - Cytology
Localized and Disseminated HS

- **Staging**
  - Abdominal u/s
  - Thoracic radiographs

- **Diagnosis:**
  - Cytology
Localized and Disseminated HS

- **Diagnosis:**
  - Histopathology with routine staining often fails to definitively diagnose this tumor type
  - Immunohistochemistry for CD18 (leukocyte marker)
Localized and Disseminated HS

- **Treatment**
  - Surgery may be an option for localized HS that has not metastasized
  - CCNU is the most effective chemotherapy agent
    - ~50% of cases will improve
- **Prognosis**
  - Negative prognostic factors: anemia, thrombocytopenia, hypoalbuminemia, splenic involvement
  - Clinical course of the disseminated for is rapid without treatment
  - For cases that improve with chemotherapy, the median survival time is 6 months
  - Dogs with localized disease treated with surgery and chemotherapy seem to do much better (MST 568 days)
Localized and Disseminated HS

- **Articular/Periarticular HS**
  - Form of localized HS
  - Lameness and joint swelling +/- other systemic signs
  - High risk of metastasis → Disseminated HS
  - Over 50% of cases in one study were Rottweilers
  - Most common sites: stifle and elbow
  - Radiographs: soft tissue swelling within and surrounding the joint, often boney lysis of one or more bones
  - Diagnosis:
    - Cytology
    - Histopathology
    - Immunohistochemistry: often required to differentiated between HS and synovial cell sarcoma
Articular/Periarticular HS

- Amputation can be considered for patients presenting with no evidence of visible metastasis on abdominal ultrasound, thoracic radiographs, and lymph node cytology.
- Preoperative diagnosis via incisional biopsy may provide prognostic information to guide decisions.

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<thead>
<tr>
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<th>Synovial Cell Sarcoma</th>
<th>Histiocytic Sarcoma</th>
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<tbody>
<tr>
<td>Metastatic Rate</td>
<td>25%</td>
<td>91%</td>
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<tr>
<td>Median Survival Time</td>
<td>30 months</td>
<td>5 months</td>
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<tr>
<td>IHC</td>
<td>Cytokeratin +</td>
<td>CD18 +</td>
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- For patients with evidence of metastasis or when amputation is declined, chemotherapy with CCNU can provide substantial palliation in many cases.
Periarticular HS - Shadow

- 7 yo SF Lab presented with right hindlimb lameness and swelling of the stifle
- TPLO 2 years prior
- Radiographs: lysis around the plate and soft tissue swelling
- Plate was removed, culture and biopsy obtained
- Culture: 1+ MRSP
- Histo: reactive changes within the bone, suspect secondary to trauma, no evidence of neoplasia
- Swelling resolved and lameness improved with antibiotics
Periarticular HS - Shadow

- Swelling and lameness recurred 3 months later
Localized HS - Shadow

- Swelling and lameness recurred 3 months later
Periarticular HS - Shadow

- Swelling and lameness recurred 3 months later
- Blood work: normal
- Abdominal ultrasound: multiple enlarged LNs
- Thoracic radiographs: normal
- Cytology obtained from the stifle mass: histiocytic sarcoma
Periarticular HS - Shadow

- **Treatment:** CCNU 60 mg/m² every 3 weeks
- **Outcome:**
  - Marked improvement in swelling and lameness
  - “Acting like a puppy again”
  - Response lasted 8.5 months and then the symptoms and swelling returned
Disseminated HS - Sonya

- 8 yo SF Golden Retriever
- 2 month history of back pain that transiently improved with rest and meloxicam
- Symptoms progressed and developed fever and poor appetite
- Blood work: mild nonregenerative anemia (0.33 RR 0.39-0.60 L/L) and hypoalbuminemia (27 RR 31-43 g/L)
Disseminated HS - Sonya

- Abdominal ultrasound: splenic and renal masses
- Thoracic radiographs: multiple pulmonary masses
• Abdominal ultrasound: splenic and renal masses
• Thoracic radiographs: multiple pulmonary masses
Disseminated HS - Sonya

- **Diagnosis:** histiocytic sarcoma
- **Treatment:** CCNU 60 mg/m² every three weeks
- **Response:**
  - Dramatic improvement in energy, comfort, and appetite
  - Thoracic radiographs improved
Disseminated HS - Sonya
Disseminated HS - Sonya
Disseminated HS - Sonya

**Outcome:**
- Peripheral lymphadenopathy developed 4 months into therapy
- Progressive HS diagnosed on LN cytology
- Therapy discontinued
Hemophagocytic HS

- Distinct form of histiocytic malignancy that arises from macrophages in the spleen and bone marrow
- Liver, lung, and lymph nodes may become involved, although discrete masses are not always present
- Clinical Signs: lethargy, weakness, anorexia
- Physical examination: pale mm, splenomegaly
- Blood work:
  - Moderate to marked regenerative anemia
  - Thrombocytopenia
  - Hypoalbuminemia
  - Hypocholesterolemia
Hemophagocytic HS

Can be confused clinically with:
- Evans Syndrome - all cases have been Coombs negative
- Splenic hemangiosarcoma – no effusion
- Diagnosis: splenic and/or bone marrow cytology
Hemophagocytic HS
Hemophagocytic HS

- **Treatment:**
  - No known effective treatment
  - Transfusion can provide temporary palliation
- **Prognosis:** grave, median survival time of 4 weeks
6 year old CM Rotti
2 week history of lethargy and poor appetite
Anemia and splenomegaly
PCV at arrival at MOVEH was 16%
Ultrasound: moderately enlarged and very irregular spleen with hypoechoic regions, no effusion, liver and lymph nodes normal
Thoracic radiographs: normal
Hemophagocytic HS - Zoro
Hemophagocytic HS - Zoro

- Hemophagocytic histiocytic sarcoma was highly suspected
- U/s guided FNA performed
- Cytology: malignant histiocytes with hemophagocytosis
- Splenectomy would not have helped resolve the anemia or symptoms
- Transfusion would have only provided temporary relief due to ongoing hemolysis
- Euthanasia elected
Histiocytic disorders comprise a wide array of clinical syndromes. A diagnosis can be made with cytology in some instances, however histopathology +/- IHC is often required. Reactive histiocytic disorders can be managed in most cases with immunosuppressive therapy targeting T cells. Localized and disseminated HS are aggressive malignancies that can rapidly progress. Dramatic but temporary improvement is possible with lomustine therapy. Hemophagocytic HS should be a differential for patients with splenomegaly and regenerative anemia.
Any Questions?