Lymphoma

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The Oncology Service
Delivering the Future of Veterinary Cancer Care

Richmond, VA
Dogwood Veterinary Referral

Springfield, VA
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Leesburg, VA
The LifeCentre
Washington, DC
Friendship Hospital Referral
Overview

• Presentation
• Stage
• Diagnostics
• Types
• Prognosis
• Treatment
• The Steroid Question
• MDRI mutants
• Novel Therapies
• Monitoring
Presentation

Cats

• Typically systemically compromised
• Mediastinal common in young Siamese FeLV positive
• Hodgkin’s-like LSA more common

Dogs

• Typically healthy
• Often presenting for PU/PD
• Two incidence peaks
  – <2 years; >10 years
• Median age 6-9 years
• Dog breeds at higher risk
  – Boxers (T cell)
  – Bull Mastiffs
  – Bassett Hounds
  – Saint Bernards
  – Scottish Terriers
  – Airedales (T cell)
  – Bulldogs
Etiology of Lymphoma - unknown

Cats

- Second hand smoking in domestic shorthair cats
- 25% of cats that test FeLV positive will develop LSA
  - Time to development 1-41 months with most developing within 5-17 months
  - FeLV integrates with myc oncogene or transduces the myc oncogene
- FIV+ cats develop LSA at 5X the rate of those not positive
- FeLV/FIV+ cats develop LSA at 80X the rate of those not positive

Dogs

- Genetics is most likely
  - Breen’s group has documented genetic mutations in golden retrievers and rottweilers associated with lymphoma
- Infectious agents have not been identified
  - Evaluated for retroviruses and helicobacter
- Environmental Factors
  - Herbicides linked to twofold increase in LSA risk
- Immunosuppression
  - ITP linked with increased risk
Substage

- a = clinically fine
- b = sick (anorexia, vomiting, diarrhea)
  - Uveitis
  - Fever
  - Hypercalcemia

Substage b historically did not have comparable survival times as substage a. This difference in response rates and survival benefit with chemotherapy is eliminated when patients are appropriately managed prior to initiating chemotherapy.

With VERY few exceptions, giving chemotherapy when a patient already feels unwell will just make the patient feel worse.
Staging

• Physical examination
  – 80% of dogs have multicentric lymphoma
• 2 View Chest Radiographs
• Abdominal Ultrasound
• CBC/Chemistry/Urinalysis
• Bone Marrow Aspirate
2 View Chest Radiographs

• 27-34% of dogs will have pulmonary changes consistent with diffuse pulmonary infiltration

• Based on bronchoalveolar lavage, incidence may be higher for pulmonary involvement

• Changes prognosis
  – Typically 6 months even if respond to multi-agent chemotherapy

• 20% of multicentric will have craniomediastinal involvement
Abdominal Ultrasound

- Hepatosplenic involvement with multicentric is common
  - Does not change prognosis

- Gastrointestinal involvement does change prognosis
  - 5-7% canine patients
  - Boxers and Shar-Peis are overrepresented and typically have epitheliotrophic T cell LSA
  - Typically only 6 months even if respond to multi-agent chemotherapy
CBC

• Anemia is the most common lymphoma-related hematologic abnormality
  – Typically normochromic and normocytic
• If myelophthisis present may have pancytopenia
• Thrombocytopenia is 30-50% of cases
  – Clinical bleeding rarely a problem
• Neutrophilia in 25-40%
• Lymphocytosis in 20%
Chemistry

• Hypercalcemia occurs in 15% of patients
  – Most common with mediastinal (30-40%)
  – Most common with T cell (35%) but can also occur with B cell

• Monoclonal gammopathies in 6%
  – Most commonly B cell
Stage

- Stage I: one lymph node
- Stage II: one side of the diaphragm
- Stage III: both sides of the diaphragm
- Stage IV: liver and spleen involvement
- Stage V: other locations or blood/bone marrow involvement
- Most oncologists will not call a renal lymphoma or a CNS LSA stage V we will call them by name as not all stage V LSAs have the same prognosis
  - Ocular and nasal can be local disease
  - Tarsal LSA in cats can be a local disease
  - CNS LSA rapidly progressive
Diagnostics

- **Cytology**
- **Histopathology**
  - Still required for many indolent forms but flow has replaced for immunophenotype and confirmation of the diagnosis
- **PARR**
  - Run on cytology
  - Flow provides more information and more rapid
- **Flow**
  - Should provide immunophenotype and cell size as well as other prognostic factors based on cell surface receptors
Cytology

Photo courtesy of Dr. LeBlanc
Histology

• Really necessary for any type of indolent lymphoma
  – Requires entire lymph node removal if suspecting indolent lymphoma
  – Except T zone which is a flow diagnosis
• Marginal or follicular lymphoma in the spleen requires splenectomy
Bone Marrow

• No longer routine for my cases as blood/bone marrow involvement does not appear to change prognosis and flow cytometry on a CBC will indicate if possible leukemia (CD34+)

• I typically assume bone marrow and not spleen causing the lymphoblasts in peripheral blood if cytopenias present on the CBC while lymphoblasts without cytopenias are likely of splenic origin
The presence of a predominant single clone is very specific (94%) for the presence of lymphoid neoplasia with a sensitivity of 75% in dogs.

It fails when the primers do not recognize the sample and the sample has to be B or T cell lymphoma which is why flow now replaces this test for me.

Detects 1:100 neoplastic cells

False positives with E. canis and lyme disease
• The primers will match up at each end of the segment and then they are run on a gel
• LSA will have one dark band because they are all one clone
• Inflammation/Infection will have a “smear” because there are all different lymphocytes in the sample
PARR

- 70-90% sensitive with a false positive rate of 5% in dogs (less sensitive in cats)
- This test should only be run if there is already a clinical suspicion that this might be lymphoma
  - i.e. run on a CBC with a lymphocytosis or questionable cells on a pathology review of a blood smear
Flow Cytometry

Figure 2: Flow cytometric plot of peripheral blood from a cat with B-cell acute lymphoid leukemia. Scatter plot of CD5 and CD21 against SSC. Lymphoid cells are positive for B-cell antigen CD21 (80% of gated cells) and negative to T-cell antigen CD5.
Flow Cytometry

• Extremely simple test to submit
  – Purple top if lymphocytosis
  – Red top with patient serum and saline and aspirate from a lymph node or other solid tumor

• This test is heavily reliant on the clinical pathologist performing this test as they must “gate” on the neoplastic population

• I use Anne Avery at CSU
  – Turn around time is typically 3-4 days

• Again this test should only be run when there is a clinical suspicion for lymphoma
  – i.e. can differentiate between lymphoma, thymoma, and idiopathic chylous effusion when run on chylous pleural effusion in a cat
CLINICAL IMMUNOLOGY REPORT FOR

Patient and Clinic Information

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Sample Information

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Results of Laboratory Tests

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<table>
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<th>Flow Cytometry Results</th>
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<tr>
<td>CD18+ lymphocytosis</td>
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Summary

The flow cytometry study revealed and expansion of large cells with intermediate expression of CD18+ (pan-leukocyte marker), however they do not have the normal scatter properties of neutrophils. The cells do not stain with any of our other common antibodies; they are negative for CD5 (T cells) and CD21 (B cells). Unfortunately we cannot further identify these cells. We would expect mast cells to be CD18+ and there is a pleomorphic mast cell tumor variant in cats which might be a consideration.

Date report generated: 10/22/2015

For questions about flow or PAIR, call Dr. Anne Avery, 970-491-1170. email (anne.avery@colostate.edu) or visit csu-cumsb.colostate.edu/academics/mip/ci-lab. For questions about billing and shipping call the Diagnostic Laboratory, 970-297-1281.
### Patient and Clinic Information

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### Flow Cytometry Study

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<td>T cell subset</td>
<td>%CD8</td>
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<td>Pan T cell</td>
<td>%CD5</td>
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<tr>
<td>B cell</td>
<td>%CD21</td>
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<tr>
<td>Monocytes</td>
<td>%CD14+</td>
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<td>Neutrophils/Myeloid</td>
<td>%CD18 high</td>
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<td>Aberrant phenotype</td>
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Immunophenotype

- Most commonly B cell in dogs
- Primary GI LSA in dogs typically T cell
- Small cell GI LSA in cats typically B cell
- Null Cell is also possible and we believe is more aggressive
  - Zeus was diagnosed 29 months ago with null cell and is still in a CR
- T cell cutaneous LSA do better than B cell cutaneous LSA
- Not prognostic in cats
Prognosis

• I no longer believe substage impacts prognosis
• I no longer believe immunophenotype impacts prognosis when CHOP-CCNU-MOPP chemotherapy elected
• Multicentric canine lymphoma has a 35% 2 year remission rate with CHOP-CCNU-MOPP
• Feline lymphoma, median survival time with COP-based chemotherapy 591 days if response noted in the first month
  – FeLV/FIV positive no longer has impact on survival
• The median survival times of dogs in the neutropenia and no neutropenia groups were 952 and 282 days, respectively
### Types of Lymphoma

#### Table 2. Epidemiological and Clinical Features of Canine Lymphomas According to the Morphological Subtypes

<table>
<thead>
<tr>
<th>Malignant Lymphoma Subtypes</th>
<th>No. Cases</th>
<th>Age in Years (Median)</th>
<th>Male</th>
<th>Female</th>
<th>Localized</th>
<th>Generalized</th>
<th>Extranodal Involvement</th>
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<td>211</td>
<td>177</td>
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<td>118</td>
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<sup>a</sup> Extranodal involvement with lymphadenopathy.
Table 6. Updated Kiel Classification of the 608 Canine Lymphomas With Possible Correlation With the World Health Organization Malignt Lymphoma Classification

<table>
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<tr>
<th>Updated Kiel Malignt Lymphoma Classification</th>
<th>No. Cases</th>
<th>% Cases</th>
<th>World Health Organization Malignt Lymphoma Classification</th>
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<tbody>
<tr>
<td>B-cell neoplasms</td>
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<td>Cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>Cutaneous T cell, high grade</td>
<td>19</td>
<td>3</td>
<td>Cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>Null-cell neoplasms</td>
<td>5</td>
<td>&lt;1</td>
<td>Natural killer-cell leukemia</td>
</tr>
</tbody>
</table>
Types of Lymphoma

- Indolent
- Lymphoblastic
- Specific anatomic locations
  - Cutaneous
  - Cardiac
  - Renal
  - Hepatosplenic
  - CNS
  - GI
Indolent Lymphoma

- Small Cell Lymphoma: prednisone/chlorambucil
- Indolent Nodular Lymphoma (Marginal, Follicular, T cell Rich B Cell Lymphoma): monitoring or prednisone/chlorambucil
- Hodgkin’s-like lymphoma: monitoring or prednisone/chlorambucil
- T-zone Indolent lymphoma: monitoring or prednisone/chlorambucil
  - Median ST 637 days (1.7 years)
  - No treatment
  - Flow diagnosis (CD4+/CD45-)
- Chronic Lymphocytic Leukemia: monitoring or prednisone/chlorambucil
Indolent LSA with veterinary literature support regarding therapy

- **Canine Splenic Marginal Zone LSA**
  - splenectomy and no clinical signs, median survival time >1,000
  - The use of chemotherapy did not impact survival

- **Canine Nodular Marginal Zone LSA**
  - Typically very responsive to chemotherapy but long term survival possible without therapy

- **Mantle Cell LSA is rare in canine patients and typically occurs in the spleen**
  - Likely getting grouped in with splenic fibrohistiocytic nodules

- **Follicular LSA is more common and appears to require treatment with multi-agent chemotherapy**
Lymphoblastic Survival Times

**Feline**

- Primary bone LSA can be treated with surgery or RT alone
- Primary ocular LSA in cats long term control with surgery or RT alone
  - Median ST with enucleation 14 months
  - Still recommend chemotherapy because some cats rapidly fail elsewhere
- LSA of large granular lymphocytes in cats really short survival times
  - median ST 57 days
- Lymphoblastic LSA in cats median ST >500 days if responders within first month of multi-agent chemotherapy

**Lymphoblastic Multicentric Lymphoma in dogs (Stage II-V)**

- 80-90% respond to chemotherapy
- Median ST 10-12 months (9-10 months reported in T cell)
- Protocol used here (L-CHOP-CCNU-MOPP) 35% CR rate at 2 years for B and T cell
Cutaneous Lymphoma

- Solitary or generalized
- Epitheliotropic (mycosis fungoides) or nonepitheliotropic
  - Mycosis fungoides is typically treated with single agent CCNU and/or safflower oil
    - Slowly progressive
  - Nonepitheliotrophic is typically B cell and treated with CHOP-based chemotherapy
    - Typically rapidly progressive
- Sezary Syndrome is when cutaneous T cell lymphoma also has these same malignant cells in circulation
  - Rapidly progressive
Typical Presentation for Mycosis Fungoides
Cutaneous Lymphoma

• Mucocutaneous of the oral cavity treated with radiation in dogs
  – Mean survival was 1129 days
  – Median survival of 770 days.
  – Overall response of radiotherapy was 67%
  – A survival advantage was seen in dogs with no evidence of lymph node metastasis and that achieved a complete response to radiation therapy
Lingual LSA

8/11/15

9/16/15
Cardiac Lymphoma

• Typically present with signs of congestive heart failure and echocardiogram is can be diagnostic
• Median remission 5.2 months
• 2 dogs long term >1yr
Renal Lymphoma

- Median survival times in cats of 3-6 months with therapy
  - 40% developed CNS signs
  - Can respond dramatically to chemotherapy but the responses are short
- 90% of dogs have bilateral involvement
- Commonly associated with CNS lymphoma
Hepatosplenic Lymphoma

- Lack peripheral lymphadenopathy
- Typically has bone marrow involvement
- Typically T cell
- Very aggressive – rarely do better than 4 months even when respond to chemotherapy
  - Case here out 3 years so long term survivors are possible
CNS Lymphoma

• If localized, radiation can be pursued
• Cytosar and CCNU penetrate the CNS but with lymphoma do not consider the blood brain barrier to be intact so typically just start with the normal CHOP-based protocols
• Marked responses are possible
  – Completely paralyzed dogs can walk again, but response duration is short (4-6 months)
  – In cats, typically 5 months but several responders lived 13 months
GI Lymphoblastic Lymphoma

• Most dogs have diffuse involvement of the intestinal tract
• Involvement of the abdominal lymph nodes and liver is common
• No difference in surgical healing when biopsies or resections performed
• Response rate ~50% with survival benefit of 6 months with multi-agent if respond
Nasal Lymphoma

• Median survival times of 1.5 years with radiation in cats
  – Cats passed 19 and 67 months from RT and no evidence of LSA
  – Median ST RT alone 593 days
  – I still recommend chemotherapy to follow as it can relapse outside the nasal cavity
    • Most commonly the kidneys

• Most common nasal tumor in cats
Intravascular Lymphoma

• Proliferation of neoplastic lymphocytes within the lumen and walls of blood vessels in the absence of extravascular sites or bone marrow involvement

• Biopsy diagnosis

• Aggressive and poorly responsive to chemotherapy
The Leukemias

• Commonly a flow diagnosis on blood now rather than requiring a bone marrow aspirate
• Chronic Lymphocytic Leukemia (CLL)
  – Long term survival with no therapy until clinical or lymphocytes greater than 50,000
  – Chlorambucil/prednisone
• Acute Lymphocytic Leukemia (ALL)
  – Treated with same multi-agent protocols as LSA
  – In the literature says 6 months, I find they do just as well as LSA if they respond to CHOP-CCNU-MOPP
• Acute Myelogenous Leukemia (AML)
  – Median survival time in the literature is less than a month
  – Routinely get 6 months of great life with doxorubicin alternating with cytosar
Prior Steroids

• Prior use of steroids does appear to correlate with shorter remission times
• <2 weeks of steroids vs. >2 weeks of steroids before starting combination chemotherapy appeared to be equally detrimental
• My personal opinion is that no pet should pass away without attempting steroids
• If all your diagnostics have been performed and samples collected there is no down side to giving steroids and often they will do better if down staged with steroids prior to initiating chemotherapy
• Steroids will cause stage migration but this is becoming of less concern amongst veterinary oncologists
• Use of steroids does promote resistance in lymphocytes via p-gp
MDR1 Mutations

• We do not think that MDR1 mutants will do worse with chemotherapy but they do require very significant dose reductions to tolerate p-gp substrate chemotherapy drugs
  – 25-50% for mutant/mutant
  – Typically start there for heterozygotes but can often dose escalate
• Breeds at risk for mutation: Collies (35% mutant/mutant)
  – Other breeds: Australian Shepherds (10% mutant/mutant), German Shepherds (2% mutant/mutant), Mixed Breeds (3% mutant/mutant), Shetland Sheepdog (1% mutant/mutant)
• Drugs that are affected by mutation: vinca alkaloids, doxorubicin, Mitoxantrone, prednisone
• Drugs not affected by development of p-gp resistance: alkylating agents
Novel Therapies

- Antibodies are becoming standard of care for certain types of lymphoma in human oncology
  - Long-term survival with rituximab for B cell LSA in people
    - Addition of rituximab improved 8-year survival from 55.9% with chemo alone to a 76.1% 8-year survival rate when rituximab added to chemo
    - Rituximab also markedly increased the median PFS (93.4 months vs. 34.9 months)
  - Chimeric monoclonal antibody against CD20
- B cell antibody is finishing up clinical trials
- T cell antibody is just starting clinical trials and TOS Richmond is a site
  - It is not free just at a discount
  - Can be used in place of chemotherapy or with traditional chemotherapy for T cell lymphoma
  - No side effects have been noted so far but the B cell antibody can cause an allergic type reaction (primarily self-limiting fever)
Monitoring

- Monthly physical examinations
- VDI TK/crp blood test
- Avacta TK/crp blood test
- Checking blood work for hypercalcemia relapse
- Repeat flow cytometry or PARR
Charlie

- Diagnosed 8/2013
- B cell
Marimba

- Diagnosed 4/2013
- T cell
Zeus

• Diagnosed 11/2012
• Saw on 10/28/15
  – 35 months
  – Still in a CR
• Not B, not T cell
  – Null cell LSA
Bruzer

- Diagnosed 8/2011
- T cell LSA/Leukemia
- Last visit 4/2015 still in CR
Current TOS Clinical Trials

- B cell antibody for canine lymphoma – closed this month
- T cell antibody for canine lymphoma – partial funding
- Chemotherapy for mammary carcinoma – fully funded (including diagnostics and staging)
Questions

• Thank you to my staff
  – Candace, Sarah, Katie, Heather, Taylor, and Michelle
  – Dr. Susan Mendez, intern extraordinaire

• Thank you to all the patients and their families

• Please do not ever hesitate to call with questions!!!!