Lymphoma – Diagnostic considerations

Lymphoma is a common but highly variable disease in dogs and cats, in terms of clinical presentations, prognosis, cyto- and histopathologic features, immunophenotype, cytogenetics, diagnostic modalities, and treatment options.

General considerations

- Multicentric lymphoma accounts for most cases. This is often large cell, and while diffuse large B cell is common, special testing must be performed to arrive at a diagnosis of T vs. B cell.
- Lymphoma can affect a variety of specific anatomic locations, in addition to peripheral lymph nodes, e.g. gastrointestinal tract, mediastinal lymph nodes, nasal cavity, kidneys, spleen, liver, CNS, etc.
- Clinical signs often are a result of clinical disease location(s) but lymphoma can also cause clinical signs that result from secondary effects of lymphoma and are unrelated to infiltrated tissues, e.g. PU/PD secondary to hypercalcemia.
- Diagnosis can be relatively straightforward, i.e. a predominance of large lymphoid cells in a lymph node, or more challenging, i.e. differentiating small cell lymphoma from inflammatory bowel disease in a cat.
- There are numerous diagnostic options, and it’s important to understand the advantages and disadvantages of these options.
- Better practices in sample collection and preparation can immediately increase the likelihood of a diagnosis.

Diagnostic options:

- **Cytology** - Used to investigate cause of lymphadenopathy, tissue masses, abnormal organs or tissues, abnormal skin lesions, and/or effusions. Also used in cases where blood work suggests underlying tissue or organ abnormalities, i.e. hypercalcemia, elevated liver enzymes, etc.
  - **Suggestions:** Practice gentle smearing of slides to maximize cell recovery. Avoid all formalin exposure or condensation on slide. Ideally, submit to clinical pathologist for evaluation - leave some slides unstained for submission but submit both.

- **Histopathology** - Biopsy (trucut, wedge, endoscopic, etc) used to evaluate masses, lymphadenopathy, abnormal tissues or organs, explain blood work changes

- **Flow cytometry** - Provides information on lymphocyte phenotype and prognosis in lymphoid neoplasms. Used in conjunction with cytoplasm, hematology, or histopathology. Requires collection of lymph node, abnormal organs, and/or fluid into a fluid medium (e.g. saline, saline + patient serum, cell media) and overnight submission to specific laboratories offering flow cytometry, e.g. Colorado State University Clinical Immunology Laboratory.

- **PCR for antigen receptor rearrangement (PARR)** - Used to determined if lymphoid population is clonal (or not) to support interpretation of lymphoid neoplasia – can be performed on cytology or histology specimens

- **Immunocytochemistry (ICC) or immunohistochemistry (IHC)** - Special technique to further characterize a neoplasm, differentiate T vs. B lymphoid cells, evaluate for some infectious etiologies in a specimen
### Comparison of diagnostic options

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<th>Cytology</th>
<th>Histopathology</th>
<th>Flow cytometry</th>
<th>Clonality – PARR</th>
<th>Immunohistochemistry (IHC) or Immunocytochemistry (ICC)</th>
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<td><strong>Advantages</strong></td>
<td>Ease of sample collection + fast turnaround.</td>
<td>Provides assessment of tissue architecture as well as provides a mitotic index, distribution of lymphoid cells. Can often differentiate small vs. large cell (although not in all tissue types). Can perform additional testing on remaining tissue blocks, i.e. IHC. Many publications based on histopathologic findings.</td>
<td>Identifies phenotype of lymphoid cells, which often provides prognostic information. Can differentiate from non-lymphoid cells, i.e. myeloid and unclassified populations (e.g. CD34+), which greatly impacts prognosis. A great test to be used with cytologic evaluation.</td>
<td>Identifies clonal expansion of lymphoid cells supporting an interpretation of lymphoma (or lymphoid leukemia). Can be performed on already-submitted and stained slides, either cytology or histopathology cases.</td>
<td>Differentiates T vs. B lymphocytes, which can have prognostic significance. May not add much additional information in some cases. T vs. B cell. Can help to confirm a diagnosis of lymphoma, if not definitive on biopsy sample.</td>
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<td>May not be able to diagnose some cases of small cell lymphoma.</td>
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<td>Must be used in conjunction with other diagnostic modalities - often follows diagnosis of lymphoma by cytology. Requires collection of additional sample into fluid + overnight shipping for evaluation. Does not prove clonality, but that may not be necessary. Additional expense.</td>
<td>Must be used in conjunction with other diagnostic modalities. Lower sensitivity, i.e. may get false negative in some animals who do have lymphoma. Also, some infectious diseases and reactive lymphoid processes can be positive, i.e. false positive. Additional expense.</td>
<td>Must be used in conjunction with other diagnostic modalities. Additional expense (per stain) on top of biopsy costs. May not provide a great deal of prognostic information. False positive or negative reactions are possible, need lab with skill in performing and reading results.</td>
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<td><strong>Disadvantages</strong></td>
<td>Poor sample collection or slide preparation or exposure to formalin can result in non-diagnostic slides.</td>
<td>Collection requires more preparation, local anesthesia or general, greater skill set. Turnaround time is longer. Expense may be greater given collection requirements. Differentiating myeloid vs. lymphoid neoplasms may not be possible without IHC.</td>
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