Reactive and Neoplastic Lymphocytosis

Koranda A. Walsh, VMD, BS
Assistant Professor, Clinical Pathobiology
University of Pennsylvania School of Veterinary Medicine

PLEASE NOTE: These notes are meant as a reference guide and are not meant to be an outline of the lecture. However, the presentation will expand upon the points included herein.

USEFUL DEFINITIONS:

**Leukemia**: The presence of neoplastic hematopoietic cells in the blood and/or bone marrow. With no modifiers, leukemia is a general term which includes leukemias of any hematopoietic lineage (i.e. lymphoid (T lymphocytes, B lymphocytes and Natural killer lymphocytes) or myeloid (erythrocyte, monocyte, granulocyte, megakaryocyte)).

**Acute leukemia**: A definition which includes neoplasia (often originating in the marrow) due to either immature myeloid or immature lymphoid cells. In these cases, morphologic features may not allow conclusive identification of cell lineage (i.e. one cannot distinguish between myeloid or lymphoid origin).

**Chronic leukemia**: Chronic designates a neoplastic proliferation of differentiated cell types (i.e. mature lymphocytes). Of the chronic leukemias chronic lymphoid leukemia is the most common.

**Leukemia associated with lymphoma (stage V lymphoma)**: Lymphoma originates outside of the bone marrow. Neoplastic cells can enter circulation (stage V lymphoma) but this does not always indicate bone marrow infiltration. If the lymphoma is small, the cells in circulation will be small. If the lymphoma is of large cells, large cells will be found in circulation.

THE INITIAL APPROACH TO LYMPHOCYTOSIS

1. First check morphology
2. Are the lymphoid cells mature or immature?
3. For mature lymphocytes, additional testing is needed (see below) to determine if the population is clonal or non-clonal
4. If they are immature and in high numbers they are most likely to represent acute lymphoid leukemia or stage V (leukemic phase) of lymphoma. In cases of small numbers of circulating immature cells, it is possible that cells which appear immature are reactive (to be discussed).
APPROACH TO SMALL/MATURE LYMPHOCYTOSIS

If the lymphocytosis is mature, as evaluated by clinical pathologist review, several steps can be taken to identify whether the population is reactive (non-neoplastic) or is neoplastic. With small/mature lymphocytes, morphology alone is not sufficient to identify reactive versus neoplastic proliferations, though certain magnitudes can increase suspicion of neoplasia. Thus additional steps must be taken to separate the two processes. These steps can include flow cytometry, establishing clonality (to be discussed in lecture), identifying chromosomal abnormalities and identifying oncogenes. The first two options are more accessible and will be expanded upon in lecture. See below for an example of an algorithm on flow cytometry in canine small lymphocytosis.
If additional testing identifies that the population is reactive (non-neoplastic) there are limited causes for a small lymphocytosis. These include physiologic (epinephrine response, which should be transient), Chronic inflammation/antigenic stimulation, young patients (often due to antigenic stimulation) and hypoadrenocorticism (see below for summary points).

**CAUSES (MAJOR) OF REACTIVE LYMPHOCYTOSIS (see charts below)**

1. Physiologic (excitement, epinephrine-induced)
2. Chronic inflammation (antigenic stimulation)
3. Young animals
4. Hypoadrenocorticism (Addison’s disease)

1. **CBC findings that support a lymphocytosis due to a physiologic response**
   - Neutrophilia (mild, mature, i.e. no left shift, normal neutrophil morphology; marginated neutrophils that have been ‘washed’ off of wall)
   - Erythrocytosis (Relative, with no evidence of dehydration e.g. splenic contraction)
- Thrombocytosis (splenic contraction)

**Chemistry findings (may or may not be present):**
- Hyperglycemia (due to epinephrine effects)

2. **CBC findings that support a lymphocytosis due to chronic inflammation (may not have all findings concurrently)**
   - Neutrophilia
   - Left shift
   - Toxic change
   - Monocytosis (inflammation, not stress given stress causes a lymphopenia)
   - Anemia of chronic/inflammatory disease (less direct support)

**Chemistry findings (may or may not be present):**
- Hyperglobulinemia

3. **CBC findings that support a lymphocytosis due to the age of the animal (antigenic stimulation e.g. recent vaccination etc. or physiologic response)**
   - Other evidence of an inflammatory leukogram or physiologic leukogram

**Chemistry findings (may or may not be present):**
- Hyperphosphatemia (elevated phosphorous) from bone growth
- ± Hypercalcemia (mild)
- ± Increased ALP

4. **CBC findings that support a lymphocytosis due hypoadrenocorticism**
   - ± Normal neutrophil count (in a stressed animal where you may expect a neutrophilia)
   - ± Eosinophilia (due to a lack of cortisol)
   - ± Mild, non-regenerative due to anemia of chronic disease or regenerative anemia (if GI bleeding)

**Chemistry findings:**
- ± Hypoglycemia (due to a lack of cortisol)
- ± Low total protein (if concurrent GI bleeding)
- ± Hypercalcemia (due to a lack of cortisol)
- ± Hyponatremia (due to a lack of aldosterone)
- ± Hyperkalemia (due to a lack of aldosterone)
- ± Pre-renal azotemia/dehydration (elevated BUN & creatinine) + poorly concentrated urine due to loss of sodium and water and a lack of urine concentrating ability, respectively (due to a lack of aldosterone)
APPROACH TO LARGE CELL/IMMATURE LYMPHOCYTOSIS
When immature cells are identified, cells may be distinctly lymphoid but it is important to know that morphology can be an insensitive indicator of lineage (i.e. morphology may not be able to distinguish in all cases between myeloid and lymphoid). If the cell morphology is cytologically unambiguous, and is thought to be lymphoid, it is either due to stage V lymphoma or lymphoid leukemia (ALL). Smear review alone cannot distinguish between stage V lymphoma or ALL. However, because prognosis can be quite different between ALL and stage V lymphoma, additional testing can be pursued to help distinguish the two. Acute lymphoid leukemias often have CD34+ on flow cytometry, are more likely to be associated with other cytopenias and lack of tissue involvement (i.e. less likely to have node enlargement or organomegaly).

5. CBC findings that support an immature lymphocytosis due to lymphoid neoplasia

| • Acute lymphoid/lymphoblastic leukemia (ALL) – An increase (mild to marked) in immature lymphoid cells which has originated in the bone marrow |
| o These cells are blasts and cannot be easily differentiated from other blasts, i.e. myeloblasts, undifferentiated blasts, so this may be termed ‘acute leukemia’ when morphology is difficult to differentiate. |
| • Stage 5 lymphoma |
| o Lymphoblasts/large lymphoid cells are seen in peripheral blood – this is uncommon (compared to the typical presentation of lymphoma). |
| o Need additional info to differentiate this from ALL (e.g. flow cytometry) |

Chemistry findings (may or may not be present):

| • ± Hyperglobulinemia in some types of B cell lymphoid neoplasms |
| • ± Hypercalcemia in some types of lymphoma |