LYMPHOMA OVERVIEW

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DEFINITION

Lymphoma is a cancer of the lymphoid cells arising in the lymphatic system
WHAT IS A LYMPHOCYTE

- Blood
  - Red Blood Cells
  - White Blood Cells
  - Platelets
    - Neutrophils
    - Eosinophils
    - Lymphocytes
    - Monocytes
    - Basophils
      - B Lymphocytes
      - T Lymphocytes
      - NK Cells
        - CD8 Cytotoxic Cells
        - CD4 Helper Cells
          - T Helper 1 cells
          - T helper 2 cells

PRESENTATION

- Lymph nodes are the most common sites of origin but they can arise from any organ in the body that has lymphoid tissue - skin, gastrointestinal tract, liver, spleen, bone marrow, brain, nasal passages
- Can arise from B cells, T cells or NK cells - all important in the immune response
LYMPHOMA IN ANIMALS

Lymphoma is the most common malignancy diagnosed in dogs – cause is mostly GENETIC
The golden retriever has a lifetime risk of 1:8 for developing lymphoma

Lymphoma is also the most common tumor seen in cats – commonly due to the association with the FELINE LEUKEMIA virus

It can occur in other animals as well including ferrets.

MAJOR TYPES

HODGKIN’S DISEASE

Nodular Lymphocyte Predominance

Classical HD

NON- HODGKIN’S LYMPHOMA

B cell lymphomas
T cell lymphomas
NK/ NK-T cell lymphomas
# HISTORICAL FACTS

## MILESTONES IN THE CLASSIFICATION OF LYMPHOID NEOPLASMS

<table>
<thead>
<tr>
<th>Year</th>
<th>Person</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1832</td>
<td>T. Hodgkin</td>
<td>First clinical report of a case of Hodgkin disease</td>
</tr>
<tr>
<td>1845, 1863</td>
<td>R. Virchow</td>
<td>Describes both leukemia and lymphoma</td>
</tr>
<tr>
<td>1898, 1902</td>
<td>C. Strenberg, D. Reed</td>
<td>Define the microscopic features of the neoplastic cells of Hodgkin Disease</td>
</tr>
<tr>
<td>1958</td>
<td>D. Burkitt</td>
<td>Describes the clinical syndrome of Burkitt’s lymphoma in African children</td>
</tr>
<tr>
<td>1956, 1966</td>
<td>H. Rappoport</td>
<td>Alternative classification for NHL</td>
</tr>
<tr>
<td>1974</td>
<td>K. Lennert</td>
<td>Proposes the Kiel classification of lymphomas - recognizes B and T cells</td>
</tr>
<tr>
<td>1975</td>
<td></td>
<td>Working Formulation proposed by the NCI</td>
</tr>
<tr>
<td>1994</td>
<td></td>
<td>Revised European–American Classification of the lymphoid Neoplasm (REAL)</td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td>WHO classification</td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td>WHO classification</td>
</tr>
</tbody>
</table>
CLASSIFICATION SYSTEMS OF NHL

- NHL classification schemes have evolved based on growing understanding of cancer cell characteristics\(^1\)
- Subclassifications are driving more specific clinical trials and therapeutic approaches\(^2\)

![Classification Diagram]

EPIDEMIOLOGY

- Most common hematologic cancer
- Prevalence ~300,000 patients
- ~53,000 new cases/year
- ~23,000 deaths/year
- Increasing incidence of non–AIDS-associated NHL
- Demographic shift accounts for most of increase
FREQUENCY OF SUBTYPES OF LYMPHOMA IN BIOPSIES

- Follicular
- Myeloma + hairy cell + lymphoblastic
- Burkitt’s
- Mantle cell
- AILD
- Immunocytoma
- Anaplastic large cell
- Peripheral T cell
- Diffuse large B cell
- Mantle cell
- SLL/CLL
- Mediastinal
- Anaplastic L Cell
- Hodgkin’s

INCIDENCE OF SUBTYPES

<table>
<thead>
<tr>
<th>LYMPHOMA SUB-TYPE</th>
<th>RELATIVE FREQUENCY</th>
<th>EST. # CASES/YEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large B-Cell</td>
<td>~ 31%</td>
<td>16,709</td>
</tr>
<tr>
<td>Follicular (I-III)</td>
<td>~ 22%</td>
<td>11,858</td>
</tr>
<tr>
<td>Marginal Zone</td>
<td>~ 8%</td>
<td>4,312</td>
</tr>
<tr>
<td>PTCL</td>
<td>~ 7%</td>
<td>3,773</td>
</tr>
<tr>
<td>Mantle Cell</td>
<td>~ 6%</td>
<td>3,234</td>
</tr>
<tr>
<td>SLL/CLL</td>
<td>~ 6%</td>
<td>3,234</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>~ 6%</td>
<td>3,234</td>
</tr>
<tr>
<td>Anaplastic L Cell</td>
<td>~ 2%</td>
<td>1,078</td>
</tr>
<tr>
<td>Hodgkin’s</td>
<td>~ 11%</td>
<td>7,500</td>
</tr>
</tbody>
</table>
SIGNS AND SYMPTOMS

- Swollen lymph nodes
- Fevers not related to infections
- Night sweats
- Itching
- Unexplained weigh loss
- Abnormal blood counts
- Elevated LDH, paraproteins in the blood
- Organ specific symptoms based on site of origin of lymphoma

CLINICAL PRESENTATIONS
RADIOLOGICAL FINDINGS

ETIOLOGY

- Infections
- Immune deficiency
  - HIV
  - Immunosuppressive agents
  - Congenital immune deficiency states
  - Post transplantation
- Environmental factors
  - Hair dyes
  - Exposure to radiation
  - Insecticides
## Infectious Agents Associated with Lymphomas

<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Type of Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epstein Barr Virus</strong></td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td></td>
<td>Post organ transplant lymphoproliferative disorder</td>
</tr>
<tr>
<td></td>
<td>Primary CNS diffuse large cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td></td>
<td>Extranodal NK/T cell lymphoma, Nasal Type</td>
</tr>
<tr>
<td><strong>HTLV-1</strong></td>
<td>Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td>Diffuse large B cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td><strong>Hepatitis C Virus</strong></td>
<td>Lymphoplasmacytic lymphoma</td>
</tr>
<tr>
<td><strong>Helicobacter Pylori</strong></td>
<td>Gastric MALT lymphoma</td>
</tr>
<tr>
<td><strong>Human Herpes Virus 8</strong></td>
<td>Primary effusion lymphoma</td>
</tr>
<tr>
<td></td>
<td>Multicentric Castleman’s disease</td>
</tr>
</tbody>
</table>

## Host Susceptibility Factors

<table>
<thead>
<tr>
<th>Type of Lymphoma</th>
<th>Host Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteropathy associated T cell lymphoma</td>
<td>Genetics, gliadin allergy</td>
</tr>
<tr>
<td>Hepatosplenic T cell lymphomas</td>
<td>EBV?</td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis</td>
<td>EBV?</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>EBV</td>
</tr>
<tr>
<td>Post transplant lymphoproliferative disorder</td>
<td>Immunosuppression, EBV</td>
</tr>
</tbody>
</table>
## DISEASES ASSOCIATED WITH AN INCREASED RISK OF LYMPHOMA

### INHERITED IMMUNODEFICIENCY STATES
- KLEINFELTER'S SYNDROME
- CHEDIAK-HIGASHI SYNDROME
- ATAXIA-TELANGEZTASIA
- COMMON VARIABLE IMMUNODEFICIENCY

### ACQUIRED IMMUNODEFICIENCY STATES
- IATROGENIC IMMUNOSUPPRESSION
- HIV-1 INFECTION
- ACQUIRED HYPOGAMMAGLOBULINEMIA

### AUTOIMMUNE DISEASES
- SJOGREN'S SYNDROME
- CELIAC SPRUE
- RHEUMATOID ARTHRITIS
- SLE

### CHEMICAL OR DRUG EXPOSURE
- PHENYTOIN
- DIGOXIN, PHENOXYHERBICIDES
- RADIATION
- PRIOR CHEMOTHERAPY
- RADIATION THERAPY

## INITIAL EVALUATION

- History and physical
- Diagnostic biopsy (excisional or incisional)
- Lab studies, CBC, diff, chem profile, LDH, B2 microglobulin, consider SPEP
- Bone marrow biopsy (bilateral?)
- Radiological studies, CT scans, PET? Gallium? MRI if indicated
- Viral serologies- hepatits B, C, HIV, HTLV1? EBV?
NOT ALL LYMPHOMAS ARE CREATED EQUAL

Log rank test: p<0.001

COMMON MARKERS FOR DIAGNOSING LYMPHOMA SUBTYPES

<table>
<thead>
<tr>
<th>T</th>
<th>B</th>
<th>NK</th>
<th>NK/T</th>
<th>HOOGKIN'S DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD 2</td>
<td>CD 20</td>
<td>CD 56</td>
<td>CD 56</td>
<td>CD 15</td>
</tr>
<tr>
<td>CD 3</td>
<td>CD 19</td>
<td>CD 16</td>
<td>CD 16</td>
<td>CD 30</td>
</tr>
<tr>
<td>CD 4</td>
<td></td>
<td></td>
<td>CD3,4</td>
<td>CD 20?</td>
</tr>
<tr>
<td>CD 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD 7</td>
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<tr>
<td>CD 10</td>
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<td></td>
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</tr>
<tr>
<td>CD 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T cell gene rearrangements</td>
<td>B cell gene rearrangements</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MATURE B CELL LYMPHOMAS

Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable*
- Splenic diffuse red pulp small B-cell lymphoma*
- Hairy cell leukemia-variant*
Lymphoplasmacytic lymphoma
Waldenstrom macroglobulinemia
Heavy chain diseases
- Alpha heavy chain disease
- Gamma heavy chain disease
- Mu heavy chain disease
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone lymphoma of mucosa-associated
Lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma*
Follicular lymphoma
Pediatric follicular lymphoma*
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma

Diffuse large B-cell lymphoma (DLBCL), NOS
- T-cell/histiocyte rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV+ DLBCL of the elderly

DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK+ large B-cell lymphoma
Plasmablastic lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
Primary effusion lymphoma
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt
B-cell lymphoma,
B-cell lymphoma unclassifiable with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

B CELL DIFFERENTIATION AND LYMPHOMA SUBTYPES

<table>
<thead>
<tr>
<th>Central lymphoid tissue</th>
<th>Peripheral lymphoid tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor B-cells</td>
<td>Pre-GC neoplasms</td>
</tr>
</tbody>
</table>
| Bone marrow             | B lymphoepithelial
| Pre-B-cell              | leukaemia/lymphoma        |
| Immature B-cell         | GC neoplasms               |
| Apoptotic B-cell        | Follicular lymphoma       |
|                        | Burkitt lymphoma           |
|                        | DLBCL (some)               |
|                        | Hodgkin lymphoma           |
|                        | Post-GC neoplasms          |
|                        | Marginal zone (MALT) lymphoma |
|                        | Cytoplasmic-plasmacytoma lymphoma |
|                        | Cell (SLL, DLBCL) (some)   |
|                        | Plasmacytoma               |

- Long-lived plasma cell
- IgM, IgA, IgG, IgD, IgE
- Naive B-cells
- Extranodal blasts
- Short-lived plasma cell
- FDC
- Memory B-cells
- Marginal zone
- Mantle cell lymphoma
- Mantle cell lymphoma
- Follicular lymphoma
- Burkitt lymphoma
- DLBCL (some)
- Hodgkin lymphoma
- Marginal zone (MALT) lymphoma
- Cytoplasmic-plasmacytoma lymphoma
- Cell (SLL, DLBCL) (some)
- Plasmacytoma
T-cell differentiation and lymphoma subtypes

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronically lymphoproliferative disorder of NK cells
Aggressive NK cell leukemia
Systemic EBV+ T-cell lymphoproliferative disease of childhood
Hydroa vacciniforme-like lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous CD4+ small/medium T-cell lymphoma
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK-
Anaplastic large cell lymphoma, ALK+
# A BIOLOGIC APPROACH TO LYMPHOMAS

| Very aggressive lymphomas | Burkitt’s lymphoma  
Diffuse large cell lymphomas – high proliferative index  
Hepatosplenic T cell lymphoma  
Blastic mantle cell lymphoma  
Gamma delta T cell lymphomas | Respond to chemotherapy and radiation therapy. Curable if treated aggressively |
|--------------------------|---------------------------------------------------------------------------------|
| Aggressive               | Diffuse large B cell lymphomas  
PTCL except cutaneous T cell lymphomas  
Mantle cell lymphoma (high ki-67)  
Transformed lymphomas         | Chemosensitive, high dose therapy and stem cell transplant can cure relapsed disease |
| Indolent                 | Follicular  
Marginal zone lymphomas, MALTS  
CTCL  
Mantle cell lymphoma (low ki-67)  
CLL/SLL                      | Slow growing, may be observed for a while. Not curable with chemotherapy alone |

# HODGKIN’S DISEASE

- **Nodular Lymphocyte Predominance** (5%)

- **Classical HD** (95%)
  - Nodular sclerosis
  - Mixed cellularity
  - Lymphocyte depletion

- **Cell type**
  - typical H/RS
THANK YOU