Historical backgrounds of classification of lymphoma and Updated Kiel classification of canine lymphoma

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Traditionally, various tumors have been classified according to their histogenesis and the degree of differentiation.

The rapid progress in immunology and molecular biology were reflected in conceptual change in the nomenclature and classification of lymphomas.

Although the microscopic appearance of lymphocytes is deceiving, T- and B-cell can be identified by newly developed methods.
Today’s menu

- **Historical backgrounds of human Non-Hodgkin’s lymphoma (NHL) classification**
- Updated Kiel classification of canine lymphomas
- Comparison of canine NHL and human NHL
### Historical changes of classification of lymphoma

<table>
<thead>
<tr>
<th>Year</th>
<th>Author/Institution</th>
<th>Classification/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1832</td>
<td>Hodgkin</td>
<td>A report of seven lymphoma cases</td>
</tr>
<tr>
<td>1940</td>
<td>Gall &amp; Mallory</td>
<td>Classification of malignant lymphoma</td>
</tr>
<tr>
<td>1966</td>
<td>Rappaport</td>
<td>Rappaport classification</td>
</tr>
<tr>
<td>1974</td>
<td>Lukes &amp; Collins</td>
<td>Lukes and Collins classification</td>
</tr>
<tr>
<td>1978</td>
<td>Lennert</td>
<td>Kiel classification</td>
</tr>
<tr>
<td>1982</td>
<td>NCI</td>
<td>Working Formulation of NHL</td>
</tr>
<tr>
<td>1994</td>
<td>Harris, et al.</td>
<td>REAL classification</td>
</tr>
<tr>
<td>2001~</td>
<td></td>
<td>New WHO classification</td>
</tr>
</tbody>
</table>
# Rappaport classification of human NHLs (1966)

<table>
<thead>
<tr>
<th>Nodular</th>
<th>VS</th>
<th>Diffuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic, well-differentiated</td>
<td></td>
<td>Lymphoblastic</td>
</tr>
<tr>
<td>Lymphocytic, poorly differentiated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed (lymphocytic and histiocytic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histiocytic</td>
<td></td>
<td>Others, Undifferentiated</td>
</tr>
</tbody>
</table>
Lukes and Collins classification of human NHLs (1974)

- **T-cell type**
  - small lymphocytic
  - sezary-mycosis fungoides
  - convoluted lymphocytic
  - immunoblastic sarcoma (T-cell)

- **B-cell type**
  - small lymphocytic
  - plasmacytoid lymphocytic
  - follicular center cell
  - immunoblastic sarcoma (B-cell)
  - histiocytic

Undefined cell type
Kiel classification of human NHLs (1978)

- **Low grade malignancy**
  - lymphocytic
  - lymphoplasmacytoid
  - centrocytic
  - centroblastic - centrocytic

- **High grade malignancy**
  - centroblastic
  - lymphoblastic
  - follicular center cell
  - immunoblastic

- Unclassified
Kiel classification of human NHLs (1978)

Conceptual figure for Kiel classification

As a means for translation of terminology among six different NHL classifications. 1175 NHL cases, 12 pathologists.

- Low grade
- Intermediate grade
- High grade
- Miscellaneous

- Architecture: Follicular, Diffuse
- Cell size: compare to RBC size
  - small 1.5-2 X RBC
  - medium 2-3 X RBC
  - large >3 X RBC
- Mitotic index

Low grade

- Small lymphocytic (CLL type, plasmacytoid)
- Follicular, predominantly small cleaved cell
- Follicular, mixed small cleaved and large cell

**Intermediate grade**

- Follicular, predominantly large cell
- Diffuse, small cleaved cell
- Diffuse, mixed small and large cell
- Diffuse, large cell

- **High grade**
  - Large cell immunoblastic
  - Lymphoblastic
  - Small non-cleaved cell
    (Burkitt’s or non-Burkitt’s)

**Miscellaneous**

- Composite
- Mycosis fungoides
- Histiocytic
- Extramedullary plasmacytoma
- Unclassifiable
- Other
Merits and drawbacks of the NCI-Working Formulation

**Merits**
- Easy to use (diagnostic histopathology)
- Based purely on morphologic assessment (predominantly architecture and cell size)

**Drawbacks**
- Most of the categories are heterogeneous
- Does not take lineage into consideration
- Prognostic groups was based on survival data from patients treated in the 1960s and 70s
- Many new entities have been recognized since the introduction of WF
Updated Kiel classification of human NHLs (1988)

- B-cell low-grade
- B-cell high-grade
- T-cell low-grade
- T-cell high-grade
Updated Kiel classification of human NHLs (1988)

- B-cell low grade
  - Lymphocytic, CLL-type
  - Lymphoplasmacytic/-cytoid (PL immunocytoma)
  - Plasmacytic
  - Centrocytic/Centroblastic
  - Monocytoid B-cell, including marginal zone cell
Updated Kiel classification of human NHLs (1988)

- **B-cell high grade**
  - Centroblastic
  - Immunoblastic
  - Large cell anaplastic Ki-1 lymphoma
  - Burkitt’s lymphoma
  - Lymphoblastic
Updated Kiel classification of human NHLs (1988)

- **T-cell low grade**
  - Lymphocytic, CLL-type
  - Small cerebriform cell (mycosis fungoides, Sézary syndrome)
  - Lymphoepithelioid (Lennert’s) lymphoma
  - Angioimmunoblastic T-cell lymphoma
  - T-zone lymphoma
  - Pleomorphic T-cell lymphoma, small cell
Updated Kiel classification of human NHLs (1988)

- **T-cell high grade**
  - Pleomorphic T-cell lymphoma, medium and large cells
  - Immunoblastic
  - Large cell anaplastic Ki-1 lymphoma
  - Lymphoblastic
Merits and drawbacks of the updated Kiel classification

**Merits**
- Easy to use (diagnostic cytology)
- Characterizes many biologically relevant entities
- Take lineage into consideration (There is good evidence that T-cell lymphomas generally are much aggressive than B-cell lymphomas)

**Drawbacks**
- The classification is mainly for nodal lymphomas
- Some categories are not reproducible
- Adult T-cell lymphoma/leukemia is not recognized as a distinct entity
- NK-cell neoplasms are not recognized
The REAL classification is not based on the histogenesis of lymphoma cells. The classification is “a list” of well defined clinicopathological entities.

<table>
<thead>
<tr>
<th>Precursor B-cell neoplasm</th>
<th>Precursor T-cell neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral (mature) B-cell neoplasm</td>
<td>Peripheral T-cell and NK-cell neoplasm</td>
</tr>
</tbody>
</table>
Merits and drawbacks of the REAL/WHO classification

Merits
- Simply a list of disease entities, thus the classification can easily be updated
- Emphasizes distinct biologic entities defined by a combination of clinical, morphologic, immunophenotypic, and genotypic feature
- High reproducibility

Drawbacks
- Often mandates immunohistochemical and/or genetic studies
- Difficult to apply the classification if clinical information is incomplete or not available
- Just a list, difficult to learn the classification
Today’s menu

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- Updated Kiel classification of canine lymphomas
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Updated Kiel classification of human NHLs (1988)

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<tr>
<td>B-cell high-grade</td>
<td>T-cell high-grade</td>
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### Updated Kiel classification of canine lymphomas, Fournel-Fleury et al. (1997)

<table>
<thead>
<tr>
<th><strong>B-cell low-grade</strong></th>
<th><strong>T-cell low-grade</strong></th>
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<tbody>
<tr>
<td>Small cell</td>
<td>Small cell</td>
</tr>
<tr>
<td>Lymphocytic</td>
<td>Clear cell</td>
</tr>
<tr>
<td>Lymphoplasmacytic</td>
<td>Prolymphocytic</td>
</tr>
<tr>
<td>Prolymphocytic</td>
<td>Pleomorphic small cell</td>
</tr>
<tr>
<td>Centrocytic</td>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>Centroblastic/centrocytic</td>
<td></td>
</tr>
<tr>
<td>Macronucleolated medium-sized cell</td>
<td></td>
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</tbody>
</table>

<table>
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<tr>
<th><strong>B-cell high-grade</strong></th>
<th><strong>T-cell high-grade</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Centroblastic</td>
<td>Pleomorphic, mixed, small and large cell</td>
</tr>
<tr>
<td>Monomorphic</td>
<td>Pleomorphic large cell</td>
</tr>
<tr>
<td>Polymorphic</td>
<td>Immunoblastic</td>
</tr>
<tr>
<td>Immunoblastic</td>
<td>Small cell, unclassifiable, plasmacytoid</td>
</tr>
<tr>
<td>Small cell, unclassifiable</td>
<td></td>
</tr>
<tr>
<td>Burkitt-type</td>
<td>Lymphoblastic</td>
</tr>
<tr>
<td>Plasmacytoid</td>
<td></td>
</tr>
<tr>
<td>Lymphoblastic</td>
<td></td>
</tr>
</tbody>
</table>

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Updated Kiel classification of canine lymphomas

**B-cell low-grade malignancy (15/92)**

- Small cell
  - Lymphocytic 0
  - Lymphoplasmacytic 2
  - Prolymphocytic 2
  - Centrocytic 1
- Centroblastic/Centrocytic 1
- Macronucleolated medium-sized cell 9

Fournel-Fleury et al. (1997)
Lymphocytic lymphoma (B-cell)
Updated Kiel classification of canine lymphomas

**B-cell high-grade malignancy (53/92)**

- Centroblastic
  - Monomorphomic 1
  - Polymorphomic 37
- Immunoblastic 13
- Small cell, unclassifiable
  - Burkitt-type 1
  - Plasmacytoid 1
- Lymphoblastic 0

Fournel-Fleury et al. (1997)
Polymorphic lymphoma with a centroblastic component,
Predominantly small-cell type (PSC)
Immunoblastic lymphoma
Updated Kiel classification of canine lymphomas

**T-cell low-grade malignancy (15/92)**

- Small cell
- Clear cell 4
- Prolymphocytic 2
- Pleomorphic small cell 2
- mycosis fungoides 7

Fournel-Fleury et al. (1997)
Updated Kiel classification of canine lymphomas

T-cell high-grade malignancy (9/92)

- Pleomorphic, mixed small and large cell 2
- Pleomorphic large cell 4
- Immunoblastic 0
- Small cell, unclassifiable, plasmacytoid 2
- Lymphoblastic 1

Fournel-Fleury et al. (1997)
Pleomorphic lymphoma (T-cell)
Lymphoblastic lymphoma, (T-cell)
Proposed choice of treatment for canine lymphomas classified by updated Kiel classification

<table>
<thead>
<tr>
<th>B-cell high-grade</th>
<th>T-cell high-grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination chemotherapy protocols</td>
<td>Combination CCNU?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B-cell low-grade</th>
<th>T-cell low-grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil or Melphalan ± Predonisolone</td>
<td>CCNU?</td>
</tr>
</tbody>
</table>

Consider no treatment unless clinical symptoms exist?
A critical feature of any tumor classification is that it be periodically reviewed and updated to incorporate new information.

In dogs, follicular lymphomas are rare, most major B-cell high grade lymphomas tend to respond better to chemotherapy. Low grade lymphomas show longer survival times without aggressive treatment.

So use of updated Kiel classification though to be better way to diagnose and treat canine lymphomas for the moment.
Special thanks to...

Dr. C. Fournel-Fleury, Ecole Vétérinaire de Lyon
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