Lymphoma Diagnostic Work-up from a Lab Perspective

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Lymphoproliferative Disorders

- Malignant lymphoma
  1. Non-Hodgkin lymphoma (NHL)
  2. Hodgkin (disease) lymphoma
  3. Multiple myeloma
Lymphomas are solid tumors of the hematopoietic system.
Neoplasms of lymphoid origin, typically causing lymphadenopathy

leukemia vs. lymphoma

- Leukemias as systemically distributed neoplasms of white cells
lymphomas and leukemias are clonal expansions of cells at certain developmental stages
B-cell development

- Stem cell
- Lymphoid precursor
- Progenitor-B
- Pre-B
- Immature B-cell
- Mature naive B-cell
- Germinal center B-cell
- Memory B-cell
- Plasma cell

Bone marrow

Lymphoid tissue
B-cell development

- Stem cell
- Lymphoid precursor
- Progenitor-B
- Pre-B
- Immature B-cell

Stages:
- Mature naive B-cell
- Germinal center B-cell
- Memory B-cell
- Plasma cell

Diseases:
- CLL
- MCL
- LBL, ALL
- DLBCL, FL, BL, HL
- MM
- MZL
- CLL

Bone marrow

Lymphoid tissue
# A practical way to think of lymphoma

<table>
<thead>
<tr>
<th>Category</th>
<th>Survival of untreated patients</th>
<th>Curability</th>
<th>To treat or not to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Indolent</td>
<td>Years</td>
<td>Generally not curable</td>
</tr>
<tr>
<td></td>
<td>Aggressive</td>
<td>Months</td>
<td>Curable in some</td>
</tr>
<tr>
<td></td>
<td>Very aggressive</td>
<td>Weeks</td>
<td>Curable in some</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>All types</td>
<td>Variable – months to years</td>
<td>Curable in most</td>
</tr>
</tbody>
</table>

- Generally defer Rx if asymptomatic
- Treat
Non-Hodgkin Lymphomas

How do we diagnose and classify these types of lymphoproliferative disorders?

- **Architectural pattern**
- **Cytologic** (cellular) morphologic appearance
- **Immunophenotypic** (antigenic) characteristics
- **Molecular** / genetic characteristics
Diagnosis requires an adequate biopsy

- Diagnosis should be biopsy-proven before treatment is initiated
- Need enough tissue to assess cells and architecture
  - open bx vs core needle bx vs FNA
Lymph Node Protocol

Permanent sections
Morphologic evaluation

Flowcytometry
Immunostains
Cytogenetics
Molecular
Flow-cytometry
Flow-cytometry

Flow cell

Dichroic Filters

Bandpass Filters

PMT 1

PMT 2

PMT 3

PMT 4

Laser

FS
Flow-cytometry
Immunostains
Non-Hodgkin Lymphomas

- Neoplasm of the immune system
- B-cells, T-cells, histiocytes
- Usually begin in the lymph nodes, but may arise in other lymphoid tissues such as spleen, bone marrow, or extranodal sites
Clinical Findings

- Enlarged, painless lymphadenopathy
- B-symptoms - fever, weight loss
- Impingement or obstruction of other structures
## Subtypes of Non-Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse Large B cell Lymphoma</td>
<td>422</td>
<td>31</td>
</tr>
<tr>
<td>Follicular Lymphoma</td>
<td>306</td>
<td>22</td>
</tr>
<tr>
<td>Chronic Lymphocytic Leukemia</td>
<td>88</td>
<td>6</td>
</tr>
<tr>
<td>Mantle Cell Lymphoma</td>
<td>83</td>
<td>6</td>
</tr>
<tr>
<td>Marginal Zone B-cell Lymphoma, MALT-type</td>
<td>72</td>
<td>5</td>
</tr>
<tr>
<td>Marginal Zone B-cell Lymphoma, Nodal</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoplasmacytic Lymphoma</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Burkitt Lymphoma</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Burkitt-like Lymphoma</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoblastic Lymphoma T/B</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral T cell Lymphoma</td>
<td>76</td>
<td>6</td>
</tr>
<tr>
<td>Anaplastic Large T-/Null cell Lymphoma</td>
<td>33</td>
<td>2</td>
</tr>
</tbody>
</table>
Most common types of lymphoma

1. Non-Hodgkin lymphoma (NHL)
   - SLL/CLL
   - Follicular lymphoma
   - Diffuse large B cell lymphoma
   - Burkitt’s lymphoma

2. Hodgkin lymphoma (HL)
Non-Hodgkin lymphoma

Incidence

Diffuse large B-cell lymphoma

Follicular lymphoma

Other NHL
General Features

**Low Grade Lymphomas**

- Adult population affected (median age, 50-70 years)
- Rare in children
- High stage disease (III/IV) is most common
- Indolent course with relatively long survival
- Generally incurable
- Transformation to higher grade NHL may occur
Small Lymphocytic Lymphoma

- Low grade B-cell malignancy
- Similar to chronic lymphocytic leukemia (CLL)
- Frequency - ~ 4% of NHL
- Older age group (median, 60.5 years)
- Bone marrow involvement: Common
- Indolent course
Flow cytometry
Follicular Lymphomas

- Frequency -~40% of NHL (most common)
- Older age group (median, 55 years)
- Often asymptomatic
- Bone marrow involvement: Common
- Indolent Course
- Chromosomal translocation, t(14;18)
Follicular Lymphomas

- Several chemotherapy options if symptomatic
- Median survival: years
- Transformation to more aggressive B-cell lymphoma
Follicular Lymphoma
Reactive Follicular Hyperplasia
# Architectural Features

## Distinguishing Reactive Follicular Hyperplasia and Follicular NHL

<table>
<thead>
<tr>
<th></th>
<th>Reactive Follicular Hyperplasia</th>
<th>Follicular NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nodal Architecture</strong></td>
<td>Preserved</td>
<td>Effaced</td>
</tr>
<tr>
<td><strong>Germinal Center</strong></td>
<td>Marked variation</td>
<td>Slight to moderate variation</td>
</tr>
<tr>
<td><strong>Size &amp; Shape</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Capsular infiltration</strong></td>
<td>None or minimal</td>
<td>Invasion with extension into pericapsular fat</td>
</tr>
<tr>
<td><strong>Density of follicles</strong></td>
<td>Low, with intervening lymphoid tissue</td>
<td>High, with back to back follicles</td>
</tr>
<tr>
<td><strong>Morphology of follicles</strong></td>
<td>Sharply defined, mantle zone</td>
<td>Ill defined, no mantle zone</td>
</tr>
</tbody>
</table>
Intermediate Grade/Aggressive

Mantle cell lymphoma

t(11;14) translocation results in over-expression of cyclin D1 protein

Diffuse large cell lymphoma
Diffuse Large Cell

- 60-70% derived from B-cells
- Often stage I or II at diagnosis
- More likely to have extranodal sites
- Peripheral blood involvement is rare
Diffuse large B-cell lymphoma
Diffuse Large B-cell Lymphoma
MIB-1
High Grade (small non-cleaved)

Burkitt lymphoma
- Endemic in Africa
- Seen in children and related to Epstein-Barr virus
- Usually extranodal

AIDS associated lymphoma
Clinical Findings

• Enlarged painless lymphadenopathy

• B-symptoms, fever, sweats, weight loss

• Impingement or obstruction of adjacent structures (mass effect)

• Extranodal presentation (30% of cases) GI tract, spleen, salivary gland
Burkitt lymphoma involving jaw

Figure 10-6. Burkitt's lymphoma in a nine-year-old child. The maxillary tumor mass is a characteristic presentation of this disease.
Burkitt lymphoma - Starry-sky pattern
Burkitt lymphoma tingible-body macrophages
High grade

- **Burkitt lymphoma**
  - Endemic in Africa
  - Seen in children and related to Epstein-Barr virus
  - B-cell phenotype
  - t(8:14) MYC/IgH
  - Usually extranodal
  - High mitotic rate (starry-sky)

- **Lymphoblastic lymphoma**
**Indolent Lymphomas**
- Very slow growing, over years.
- Follicular lymphoma, grades I/II is prototype.
- If can’t cure, goal is to control disease/symptoms.
- Decision of WHEN to treat is important.

**Aggressive Lymphomas**
- Rapidly growing, over days, months.
- Diffuse large B cell lymphoma is prototype.
- Cure is possible.
- About 50% with multi-agent chemotherapy.