Understanding Lymphoma from a Lab Perspective

Mohamed E. Salama M.D.

Medical Director, Hematopathology and Immunoperoxidase Staining
ARUP Laboratories
Lymphoproliferative Disorders

- Malignant lymphoma
  1. Non-Hodgkin lymphoma (NHL)
  2. Hodgkin (disease) lymphoma
  3. Multiple myeloma
Basic concepts

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.
NORMAL LYMPH NODE

- Follicle / germinal center (B cell)
- Mantle zone (B-cell)
- Paracortex (T-cell)
- Medullary cord (B-cell)
- Lymphatic sinus
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

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

Lymphoid tissue
Origin of lymphoid neoplasms

- B cell neoplasms
  - Precursor B lymphoblastic lymphoma/leukemias
  - Small lymphocytic lymphoma
  - Chronic lymphocytic leukemia
  - Multiple myeloma
- T cell neoplasms
  - Precursor T lymphoblastic lymphoma/leukemias
  - Bone marrow
    - CLP
    - BLB
    - NBC
    - PC
  - Thymus
    - DN
    - DP
    - CD4
    - CD8
- Lymph node
  - Mantle cell lymphoma
  - Follicular lymphoma
  - Burkitt lymphoma
  - Diffuse large B cell lymphoma
  - Hodgkin's lymphoma
  - Diffuse large B cell lymphoma
  - Marginal zone lymphoma
  - Small lymphocytic lymphoma
  - Chronic lymphocytic leukemia

Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition. Copyright © 2009 by Saunders, an imprint of Elsevier, Inc. All rights reserved.
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>
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<tbody>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Indolent</td>
<td>Years</td>
<td>Generally not curable</td>
</tr>
<tr>
<td>Aggressive</td>
<td>Months</td>
<td>Curable in some</td>
<td>Treat</td>
</tr>
<tr>
<td>Very aggressive</td>
<td>Weeks</td>
<td>Curable in some</td>
<td>Treat</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>
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

CD20

Detection enzyme

AntiCD20 antibody
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 4: WHO classification of the mature B-cell, T-cell, and NK-cell neoplasms (2008)

<table>
<thead>
<tr>
<th>Mature B-cell neoplasms</th>
<th>Mature T-cell and NK-cell neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lymphocytic leukemia/small lymphocytic lymphoma</td>
<td>T-cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>B-cell prolymphocytic leukemia</td>
<td>T-cell large granular lymphocytic leukemia</td>
</tr>
<tr>
<td>Splenic marginal zone lymphoma</td>
<td>Chronic lymphoproliferative disorder of NK cells*</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>Aggressive NK cell leukemia</td>
</tr>
<tr>
<td><strong>Spinal lymphoma/leukemia, unclassifiable</strong> Spinal diffuse red pulp small B-cell lymphoma</td>
<td>Systemic EBV+ T-cell lymphoproliferative disease of childhood</td>
</tr>
<tr>
<td>Hairy cell leukemia-variant*</td>
<td>Hydroa vacciniforme-like lymphoma</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
<td>Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td>Waldenström macroglobulinemia</td>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>Heavy chain diseases</td>
<td>Enteropathy-associated T-cell lymphoma</td>
</tr>
<tr>
<td>Alpha heavy chain disease</td>
<td>Hepatosplenic T-cell lymphoma</td>
</tr>
<tr>
<td>Gamma heavy chain disease</td>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>Mu heavy chain disease</td>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>Plasma cell myeloma</td>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>Solitary plasmacytoma of bone</td>
<td>Primary cutaneous CD30+ T-cell lymphoproliferative disorders</td>
</tr>
<tr>
<td>Extraskeletal plasmacytoma</td>
<td>Lymphomatoid papulosis</td>
</tr>
<tr>
<td>Extramedullary marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)</td>
<td>Primary cutaneous anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>Nodal marginal zone lymphoma</td>
<td>Primary cutaneous gamma-delta T-cell lymphoma</td>
</tr>
<tr>
<td>Pediatric nodal marginal zone lymphoma</td>
<td>Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma*</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>Primary cutaneous CD4+ small/medium T-cell lymphoma*</td>
</tr>
<tr>
<td>Pediatric follicular lymphoma</td>
<td>Periipheral T-cell lymphoma, NOS</td>
</tr>
<tr>
<td>Primary cutaneous follicular center lymphoma</td>
<td>Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>Anaplastic large cell lymphoma, ALK+</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma (DLBCL), NOS T-cell/histiocyte-rich large B-cell lymphoma EBV+ DLBCL of the elderly DLBCL associated with chronic inflammation</td>
<td>Anaplastic large cell lymphoma, ALK+</td>
</tr>
<tr>
<td>Primary mediastinal (thymic) large B-cell lymphoma</td>
<td>Primary cutaneous anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>Intravascular large B-cell lymphoma</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Primary cutaneous DLBCL, leg type</td>
<td>Nodular lymphocyte-predominant Hodgkin lymphoma</td>
</tr>
<tr>
<td>ALK+ large B-cell lymphoma</td>
<td>Classic Hodgkin lymphoma</td>
</tr>
<tr>
<td>Plasmablastic lymphoma</td>
<td>Nodular sclerosis classic</td>
</tr>
<tr>
<td>Large B-cell lymphoma arising in HHV8–associated multicentric Castlemann disease</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>Lymphocyte-rich classic</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma</td>
<td>Mixed cellularity classic Hodgkin lymphoma</td>
</tr>
<tr>
<td>B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma</td>
<td>Lymphocyte-depleted classic Hodgkin lymphoma</td>
</tr>
</tbody>
</table>

* Provisional entities for which the WHO Working Group thought there was insufficient evidence to recognize as distinct diseases at this time.

†These lesions are classified according to the leukemia or lymphoma to which they correspond. Diseases shown in italics were newly included in the 2008 WHO classification.
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 Lymphomas

Incidence

- Diffuse large B-cell lymphoma
- Follicular lymphoma
- Other NHL
General Feature

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)
- Transformation to more aggressive B-cell lymphoma
Follicular Lymphoma
Reactive Follicular Hyperplasia
Follicular Lymphoma

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

- No standard approach proven better than others
  - Treatment individualized accounting for lymphoma and patient characteristics, co-morbidities, etc

- Local irradiation for localized symptoms

- Systemic treatment for systemic disease
  - Chemotherapy, single agent or combination
    - Combination = better responses at expense of increased toxicity

- Monoclonal antibodies
  - Rituximab
  - Single most important breakthrough in B-cell NHL treatment
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
Prognosis

- Cell of origin
  - IHC – CD10, BCL6 & MUM-1
- BCL2 / MYC expression
DLBCL Prognostic Testing

A

B

MYC IHC

BCL2 IHC
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)
- Could be HIV associated

Lymphoblastic 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
Burkitt lymphoma - Starry-sky pattern
Burkitt lymphoma tingible-body macrophages
Combination chemotherapy is mainstay of therapy

R-CHOP is proven standard
- Rituximab
- Cyclophosphamide
- Hydroxdaunomycin = doxorubicin
- Oncovin = vincristine
- Prednisone

Additional treatment depending upon individual circumstances:
- XRT for bulky lesions
- CNS prophylaxis with IT chemotherapy (MTX, ara-C)
  - if liver, BM, testicular, sinus involvement or multiple extra-nodal sites

CURE is the goal!
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.
Staging of lymphoma

Stage I

Stage II

Stage III

Stage IV

A: absence of B symptoms
B: fever, night sweats, weight loss
Lymphoproliferative Disorders

• Malignant lymphoma
  1. Non-Hodgkin lymphoma (NHL)
  2. Hodgkin (disease) lymphoma
  3. Multiple myeloma
Hodgkin lymphoma

Thomas Hodgkin
(1798-1866)
Hodgkin lymphoma

- Reed-Sternberg cells are the tumor cells

- Large numbers of “reactive” cells are also seen in the background
Reed-Sternberg Cells in a Reactive Background
Reed Sternberg Cells

CD30 and CD15 positive

CD30
Clinical Findings

- Males > Females
- Bimodal age distribution 15-45 years old and > 50 years old
- Painless enlargement of lymph nodes, usually in neck
- Constitutional symptoms are common
- Extranodal disease is rare
Mediastinal involvement by HL is common
Subtypes of Hodgkin Lymphoma

- Classical Hodgkin Lymphoma
  - Nodular sclerosis 60-80%
  - Mixed cellularity 15-30%
  - Lymphocyte-rich 5-6%
  - Lymphocyte-depleted <1%

- Lymphocyte predominant, nodular HL 4-5%
Thank you