Diffuse Large B-cell Lymphoma, Burkitt Lymphoma and the Gray Zone

L. Jeffrey Medeiros, M.D.
M.D. Anderson Cancer Center

Relative Frequency of B-cell NHL

- Diffuse large B-cell lymphoma: 37%
- Follicular lymphoma: 29%
- Small lymphocytic lymphoma/CLL: 12%
- MALT lymphoma: 9%
- Mantle cell lymphoma: 7%
- Burkitt lymphoma: 0.8%

2008 WHO book, p. 164

Diffuse Large B-cell Lymphoma

Definition

DLBCL is a neoplasm of large B lymphoid cells with nuclear size equal to or exceeding normal macrophage nuclei that has a diffuse growth pattern

2008 WHO book, p. 233
The definition of DLBCL is like an old car

You can drive it but...

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**Diffuse Large B-cell Lymphoma**

**Clinical Findings**

- Median age: 64 y (wide range)
- Male: 55%
- Stage I-II: 54%
- III-IV: 46%
- B symptoms: 33%
- BM involved: 16%
- IPI 0-1: 35%
- 2-3: 46%
- 4-5: 19%

*Nebraska NHL Classification Project*

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**Diffuse Large B-cell Lymphoma NOS**

**Morphologic Variants**

<table>
<thead>
<tr>
<th>Common</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centroblastic (90%)</td>
<td>Sinusoidal</td>
</tr>
<tr>
<td>Immunoblastic (10%)</td>
<td>Spindled</td>
</tr>
<tr>
<td>Multilobated (&lt;5%)</td>
<td>Myxoid</td>
</tr>
<tr>
<td>Anaplastic (&lt;5%)</td>
<td>Signet Ring</td>
</tr>
<tr>
<td></td>
<td>Rosettes</td>
</tr>
</tbody>
</table>
Diffuse Large B-cell Lymphoma

CHOP vs. Other Chemotherapy Regimens

Groupe d'étude des lymphomes de l'adulte (GELA) (n=399)

R-CHOP is Better than CHOP

Groupe d'étude des lymphomes de l'adulte (GELA) (n=399)

DLBCL is a “Wastebasket” Category

De novo

Nodal or extranodal

Transformation from

CLL/SLL, FL, MZL, NLPHL

Spectrum of immunophenotypic features

GC vs. ABC

Viral causes

EBV, HHV8
## Diffuse Large B-cell Lymphoma
### International Prognostic Index

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≤ 60 vs. &gt;60 years</td>
</tr>
<tr>
<td>Performance status</td>
<td>0-1 vs. 2-4</td>
</tr>
<tr>
<td>LDH elevated</td>
<td>Normal vs.</td>
</tr>
<tr>
<td>Extranodal sites</td>
<td>≤ 1 vs. &gt;1 site</td>
</tr>
<tr>
<td>Stage</td>
<td>I-II vs. III-IV</td>
</tr>
</tbody>
</table>


## Diffuse Large B-cell Lymphoma
### Gene Expression Profiling Using DNA Microarrays

*Ash Alizadeh, MD, PhD*

- Lymphochip with 17,856 cDNA clones
- 12,069 Germinal center B-cell genes
- 2,338 B-cell NHL genes
- 3,186 Activated lymphocyte genes

*Louis Staudt, MD, PhD*

*Nature 403: 503, 2000*

## Diffuse Large B-cell Lymphoma
### Gene Expression Profiling

*Nature 403: 503, 2000*
Diffuse Large B-cell Lymphoma
Gene Expression Profiling

Three types of DLBCL
Germinal center-like
Activated B lymphocyte-like
Poorly defined / PMBCL \( \{ \text{non GC} \)
**Diffuse Large B-cell Lymphoma**

Gene Expression Data is Valid for R-CHOP Treated Patients

R-CHOP Therapy


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**Can Immunohistochemistry be used as a Surrogate for GEP in DLBCL?**

Blood 106: 275, 2004

Results match gene expression profile in 76% of cases

Chris Hans, MD

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**Immunohistochemical Methods for Predicting Cell of Origin and Survival in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP**


Results match gene expression profile in ~90% of cases

J Clin Oncol 29: 2, 2011
Whole exome sequencing of 6 cases of DLBCL
Copy number analysis using SNP arrays
DLBCL carry ~ 30 gene mutations
New abnormalities identified in:
  Chromatin methylation (MLL)
  Immune surveillance

Gene Mutations in DLBCL
Potential Impairment of Many Cellular Processes

Transcriptional regulation (p53)
Lymphocyte activation (STAT6, BCL10)
Lymphocyte differentiation (NF-κB, PRDM1)
Histone methylation (EZH2, MLL2)
Histone acetylation (CREBBP, MEF2B)
Immune surveillance (B2M)
**Diffuse Large B-cell Lymphoma**

**Clinical Features of GC and ABC Tumors**

<table>
<thead>
<tr>
<th></th>
<th>GC</th>
<th>ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>~40%</td>
<td>~60%</td>
</tr>
<tr>
<td>5-year OS</td>
<td>59%</td>
<td>30%</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>t(14;18)/IGH-BCL2</td>
<td>t(3q27)/BCL6 Trisomy 3 del(6q)</td>
</tr>
<tr>
<td></td>
<td>t(3q27)/BCL6 MYC translocations</td>
<td></td>
</tr>
<tr>
<td>Gene mutations</td>
<td>MLL, EZH2, PTEN</td>
<td>A20/TNFAIP3, CARD11, MYD88, CD79B</td>
</tr>
<tr>
<td>Mechanisms</td>
<td>BCL-2/apoptosis</td>
<td>NF-κB activation</td>
</tr>
<tr>
<td></td>
<td>Chromatin modulation</td>
<td>B-cell receptor signaling</td>
</tr>
<tr>
<td></td>
<td>PI3K/AKT activation</td>
<td></td>
</tr>
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</table>

Nature Genetics 43: 830, 2011

**Diffuse Large B-cell Lymphoma**

12 types in WHO

Primary mediastinal B-cell lymphoma
Primary DLBCL of the CNS
Primary cutaneous DLBCL, leg type
T cell/histiocyte-rich large B-cell lymphoma
Plasmablastic lymphoma
Intravascular large B-cell lymphoma

**Diffuse Large B-cell Lymphoma**

12 types in WHO

ALK+ large B-cell lymphoma
Primary effusion lymphoma
Lymphomatoid granulomatosis
DLBCL associated with chronic inflammation
DLBCL in HHV8+ multicentric Castleman disease
EBV+ DLBCL of the elderly
Primary Mediastinal Large B-cell Lymphoma

Important Points

Younger patients; women > men
Big mediastinal mass; probably thymic origin
Cervical and supraclavicular LNs can be involved
Current criteria for dx are clinicopathologic
   Not perfect
   Typical DLBCL can involve mediastinum

Primary DLBCL of the CNS
Primary DLBCL of the CNS

Important Points

What is essential to definition?

- Intrinsic biology of tumor
- Blood-brain barrier
- Combination of the two

Patients with immunodeficiency are excluded

Primary Cutaneous DLBCL, Leg Type

Can affect any skin site
- Lower legs #1

These tumors are activated B-cell type
- MUM1+ FOXP1+ BCL6+ CD10-

Chemotherapy is required
- In contrast with cutaneous FL
**T cell/histiocyte-rich large B-cell lymphoma**

**Important Points**

- Patients present with fever, malaise and hepatosplenomegaly
- High International Prognostic Index (IPI)
- Common bx specimens: Liver, bone marrow, abdominal LNs
- Often refractory to standard chemotherapy

**Plasmablastic Lymphoma**

**Important Points**

- Patients present with fever, malaise and hepatosplenomegaly
- High International Prognostic Index (IPI)
- Common bx specimens: Liver, bone marrow, abdominal LNs
- Often refractory to standard chemotherapy
Plasmablastic Lymphoma
Part of a Spectrum of B-Cell Differentiation

Important Points
- Usually associated with immunodeficiency
  - HIV
  - Transplantation
  - Iatrogenic
- Typically extranodal disease
- Immunophenotype is that of plasma cells
  - CD138+, MUM1+, CD20-
  - EBER usually +
- Grouped with DLBCLs – should it be?

Intravascular Large B-cell Lymphoma
Bone Marrow
ALK-Positive Large B-cell Lymphoma
IgA+, EMA+, CD30-, CD20-t(2;17)(p23q23)

Relative Frequency of B-cell NHL

<table>
<thead>
<tr>
<th>Lymphoma Type</th>
<th>Frequency</th>
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<tr>
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<td>37 %</td>
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<td>Burkitt lymphoma</td>
<td>0.8 %</td>
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2008 WHO book, p. 164

A SARCOMA INVOLVING THE JAWS IN AFRICAN CHILDREN
By DENIS BURKITT
From the Department of Surgery, Makerere College Medical School, and Mulago Hospital, Kampala, Uganda

Denis Burkitt

**Burkitt Lymphoma**

*Endemic*
- Equatorial Africa
- Primarily children, male predominance
- Extranodal sites common - jaw, gonads, abdomen
- >90% EBV+

*Sporadic*
- Western countries
- Peaks in childhood and elderly, male predominance
- Abdomen common site
- ~20% EBV+

*Immunodeficiency-associated*
- 20-40% EBV+

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**Burkitt Lymphoma**

**Histologic Features**

- Prominent starry-sky pattern
- Intermediate cell size
- Nuclear size approximates that of histiocyte nucleus
- 2-5 nucleoli
- Numerous mitoses

**Endemic, sporadic, and immunodeficiency-associated types are indistinguishable**

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**Burkitt Lymphoma / Leukemia**

[BM smear image]

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**Burkitt Lymphoma**

**Translocations**

- t(8;14)(q24;q32) - IgH (80%)
- t(8;22)(q24;q11) - Igκ (15%)
- t(2;8)(p11;q24) - Igκ (5%)

- **MYC**
  - Chromosome 8q24
  - BHLH transcription factor
  - Growth /proliferation/survival

- **Mechanism**
  - Overexpression of MYC

---

**Burkitt Lymphoma**

**Recent Trends in Diagnosis**

- **Less of an emphasis on perfect morphology**
  - Some atypical features are OK

- **Immunophenotype more important**
  - CD10+, BCL-6+, Ki-67 >95%
  - BCL-2-

- **Cytogenetics should be relatively simple**
  - t(8;14) or variant MYC translocations
  - ≤2 other abnormalities

---

**MYC Translocations Are Not Specific**

- **Neoplasms with MYC Rearrangement**
  - CLL in prolymphocytic transformation
  - B-cell prolymphocytic leukemia
  - Mantle cell lymphoma, blastoid variant
  - Follicular lymphoma, transformed
  - Diffuse large B-cell lymphoma (≈10%)

- **MYC rearranges with Ig or non-Ig gene partners**
Molecular Diagnosis of Burkitt’s Lymphoma

Sandeep S. Date, M.D., Kai Fu, M.D., Ph.D., George W. Wright, Ph.D., Lloyd T. Lee, Ph.D., Philip Klink, M.D., Everjan Bremma, B.S., Timothy C. Cohen, M.D., Donna D. Weinstein-Lipple, M.D., Andreas Reschewski, M.D., German-Otto M.D., Hans-Konrad Moller-Hemmelis, M.D., Randy D. Gassman, M.D., Jan Offiah, M.D., Lisa M. Wicen, M.D., Rita M. Bispel, M.D., Thomas M. Cogan, M.D., Elisa Campol, M.D., Elaine S. Jeffe, M.D., Bhavika J. Date, Ph.D., Warren Sanger, Ph.D., Martin Bos, B.S., Julie W. Voss, M.D., James R. Amelio, M.D., Joseph M. Conner, M.D., Erland B. Smeland, M.D., Ph.D., Steen Kusiak, M.D., Ph.D., Harold Holle, M.D., Ph.D., Richard R. Fisher, M.D., Thomas F. Miller, M.D., Emilio Montesano, M.D., Wyndham Hill, M.D., Ph.D., Ph.D., Manika Bhat, B.S., Hong Zuo, M.E., Lijing Yang, Ph.D., John Powell, M.S., Richard Simon, D.Sc., Wing C. Chan, M.D., and Louis M. Staud, M.D., Ph.D., for the Lymphoma/Leukemia Molecular Profiling Project


<table>
<thead>
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<th>Tumor Classification of Cases†</th>
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<tr>
<td>Tumor Type</td>
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<tr>
<td>Burkitt’s lymphoma</td>
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The pathology of lymphoma is evolving. The World Health Organization (WHO) classification of lymphomas is based on morphologic, immunophenotypic, and genetic findings.

Haematologica 93: 1327, 2008

“Discrepant” Burkitt Lymphoma

Maybe not Burkitt?

Older patients
Male = Female

1(14;18) in 3/5

BCL-2+ in 2 cases

Many genomic imbalances
Aggressive lymphomas that have morphological and genetic features of both DLBCL and BL, but for biological and clinical reasons should not be included in these categories.

This is a heterogeneous category that is not considered a disease entity but is useful in allowing classification of cases not meeting criteria for BL or DLBCL.
# Prognostic Value of MYC Rearrangement in Cases of B-Cell Lymphoma, Unclassifiable, With Features Intermediate Between Diffuse Large B-Cell Lymphoma and Burkitt Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>57 yo</th>
<th>(18-80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57/52</td>
<td>(71%)</td>
</tr>
<tr>
<td>Male</td>
<td>37/52</td>
<td>(71%)</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>32/52</td>
<td>(62%)</td>
</tr>
<tr>
<td>Performance status &gt;2</td>
<td>15/52</td>
<td>(29%)</td>
</tr>
<tr>
<td>LDH &gt;2 normal</td>
<td>18/52</td>
<td>(35%)</td>
</tr>
<tr>
<td>IPI &gt;3</td>
<td>28/52</td>
<td>(54%)</td>
</tr>
</tbody>
</table>

Cancer 2011 (in press)

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# Double Hit B-cell Lymphoma

**Definition**

Lymphomas with recurrent chromosomal breakpoints activating multiple oncogenes - one of which is MYC

- MYC + BCL-2
- MYC + BCL-6
- MYC + BCL-2 + BCL-6 (triple hit)
- MYC + BCL-3
- MYC + CCND1

Blood 117: 2319, 2011

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# B-Cell Lymphoma, Unclassifiable, with Features Intermediate Between DLBCL and BL

**MYC Predicts Poorer Survival**

- blood 117: 2319, 2011
**MYC+ BCL2+ Double Hit Lymphoma**
Clinical Features of Cases at MDACC

Median: 55 years (18-76)

- 82% LDH high
- 73% Stage III/IV
- 63% IPI >2
- 58% BM +
- 55% >2 extranodal sites
- 26% CSF +
- 20% history of FL

Mod Pathol 2011 (in press)

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**Double Hit B-cell lymphoma**
Morphologic Features

- 29 (56%) BCLU, with features intermediate between DLBCL and Burkitt lymphoma
- 19 (36%) Diffuse large B-cell lymphoma
- 2 (4%) Follicular lymphoma, grade 3
- 1 (2%) B-lymphoblastic lymphoma
- 1 (2%) Composite B-LBL and DLBCL

98% of cases had GC B-cell immunophenotype
When to consider double hit tumor?
- Aggressive histology (e.g. starry sky)
- B-cell lineage
- BCL-2 expression
- Ki-67 high

Our approach to the diagnostic line of report
- Genetic findings followed by morphology
  - e.g. B-cell lymphoma with MYC and BCL2 c/w...

Diffuse Large B-cell Lymphoma
- Features Suggestive Aggressive Disease
  - Starry sky pattern
  - High mitotic rate
  - High apoptotic rate
  - High proliferation rate

Diffuse Large B-cell Lymphoma
- Closing Comment
  - The current definition is too simple
  - It is being refined
  - We were here...
  - We want to be here...