Diffuse Aggressive B-cell Lymphomas

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Diffuse Aggressive B-cell Lymphomas

• Diffuse Large B-cell lymphoma
  - Nucleus equal or exceeding a normal macrophage nucleus or more than 2X the size of a small lymphocyte

• Burkitt Lymphoma
  - Nucleus slightly smaller than a histiocyte nucleus

WHO 2008
Diffuse Large B-cell Lymphoma

- Most common histologic subtype (30% adult NHL in the west and higher in developing countries)
- Occur at any age including childhood, median 64 years
- Slightly more common in males
- Marked histologic and biologic diversity
- Spontaneously aggressive and even with improved therapy 40% not cured
DLBCL

- De Novo (primary)
- Progression or transformation from:
  - CLL/SLL (Richter’s syndrome)
  - Follicular lymphoma
  - NLPHL to TCRBCL or DLBCL
  - Marginal Zone Lymphoma
- Immunodeficiency is a risk factor and about 10% DLBCL are EBV+
Progression of FL to DLBCL

- FL grade 3 with diffuse areas containing >15 Centroblasts/HPF warrants separate diagnosis of DLBCL
- Staining for dendritic cells (CD23/CD21+) may be essential to distinguish large or confluent follicles from DLBCL
DLBCL Clinical Features

- Extranodal (>40%) (Stage I or II) or nodal rapidly enlarging mass.
- Stomach, ileocecal region, bone, testis, spleen, Waldeyer’s ring, salivary gland, thyroid, liver, kidney, adrenal
- Long term remission rate 50-60% improved with rituximab. Overall 5-yr survival 46%, failure free survival 41%
Unfavorable Variables in DLBCL

• Age >60 years
• Poor performance status (ECOG>2)
• Advanced stage (III-IV)
• Extranodal involvement >2 sites
• High serum LDH
# Diffuse Aggressive B-cell Lymphomas

## Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>DLBCL (30%)</th>
<th>Burkitt (3%) and B-Lymphoblastic (&lt;1%)</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Usually older but any age</td>
<td>Children, Young Adults</td>
</tr>
<tr>
<td><strong>Growth rate</strong></td>
<td>Fast</td>
<td>Very fast</td>
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<td><strong>Stage</strong></td>
<td>Even distribution (50% Stage 1 or 2)</td>
<td>Usually high stage</td>
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<tr>
<td><strong>Blood or Marrow Involvement</strong></td>
<td>Uncommon, Often Terminal</td>
<td>Common</td>
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<td><strong>CNS involvement</strong></td>
<td>Unusual- New WHO category DLBCL of the CNS</td>
<td>Common</td>
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<td><strong>Response to treatment</strong></td>
<td>60-80% response</td>
<td>Up to 85-95% response</td>
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DLBCL Diagnosis Usually Easy:

- Sheets of large cells
- B-cell phenotype
- Small T-lymphocytes/histiocytes usually present (but do not confuse with TCRBCL)
- Sclerosis may be prominent
- Mitotic figures easily identified.
But diagnosis may be Difficult When:

- Mimics other neoplasms, may be cohesive or involve sinusoids, mimicking carcinoma, melanoma
- Lacks CD20 (Plasmablastic, ALK+ DLBCL)
- Shares aspects with other lymphomas, probably due to common pathogenic pathways (Burkitt-like, Hodgkin-like, Grey zone lymphomas)
- Don’t look like DLBCL (T-cell/Histiocyte rich lymphomas or presence of RS cells especially EBV+ cases)
Differential diagnosis

- Carcinoma
- Germ cell tumor
- Burkitt lymphoma variants
- Blastoid mantle cell lymphoma
- Granulocytic sarcoma
  - Myeloperoxidase, lysozyme, CD43+
Nasopharyngeal carcinoma resembling DLBCL
Neuroendocrine Carcinoma Mimicking DLBCL
Germ Cell Tumor Mimicking DLBCL

OCT3/4
Bone marrow biopsy DLBCL?
DLBCL Immunophenotype

- Pan B-cell markers CD19, D20, CD22, CD79a, PAX5
- Surface/cytoplasmic Ig (IgM>IgG>IgA) in 50-75% of cases
- CD30 variable, positive in anaplastic variant
- Complete B-cell program including expression of OCT-2 and BOB.1
- Other markers
  - CD10 40%
  - bcl-6 60%
  - BCL2 50%
  - CD43 20%
  - CD5 <10%
  - CD30+ 10%
  - MUM1 40%
  - P53 30%
  - Ki67 40-90%
Aberrant phenotypes in DLBCL

- Often lack one or more B-cell markers CD19, CD20, CD22, CD79a
- Co-expression of MUM1 and BCL6 (unlike normal germinal centers)
- BCL6+ without t(14;18)
- CD3+ DLBCL
- CD5+ DLBCL
- Cyclin D1+ DLBCL
  - Ehringer Am J Clin Pathol 2008 129-630: 231 cases of de novo DLBCL 4% cyclin D1+, CD5-
  - Extra copies of cyclin D1 may be due to trisomy of CCND1/chromosome 11
DLBCL Genetics

- Clonal rearrangements of immunoglobulin heavy and light chain genes
- Somatic hypermutations in the variable regions
- Most common genetic findings
  - 30% abnormalities in 3q27 involving BCL6
  - BCL2 t(14;18) 20%
  - MYC rearrangement 10%
## Common Molecular Events

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<th>Percentage</th>
<th>Location</th>
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<tr>
<td>BCL6 (3q27) ABC&gt;GC</td>
<td>35-40%</td>
<td>3q27</td>
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<tr>
<td>BCL2 (18q21) GC</td>
<td>40%</td>
<td>14;18</td>
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<tr>
<td>C-MYC (8q24) GC</td>
<td>10%</td>
<td>t(8;14)</td>
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<td>t(8;22)</td>
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<td>t(8;?)</td>
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DLBCL Variants, Subgroups, and Subtypes /Entities (WHO 2008)

- Diffuse Large B-cell Lymphoma NOS
- Diffuse Large B-cell Lymphoma Subtypes
- Other Lymphomas of Large B-cells
- Borderline cases
  - B-cell lymphomas unclassifiable
DLBCL Not otherwise Specified (NOS) WHO 2008

- **Common Morphologic variants**
  - Centroblastic
  - Immunoblastic
  - Anaplastic

- **Rare Morphologic variants**
  - Spindle cell, signet ring cell, microvillous projections etc.

- **Molecular subgroups**
  - Germinal centre B-cell like (GCB)
  - Non-germinal centre B-cell like (non-GCB)

- **Immunohistochemical subtypes**
  - CD5+ DLBCL
DLBCL NOS Centroblastic Variant

- Most common variant
- Cells intermediate to large with round or oval nuclei, vesicular chromatin, 2-4 nucleoli often at the nuclear membrane
- Moderate amphophilic to basophilic cytoplasm
- May be monomorphc centroblasts or admixed with immunoblasts
- Nuclei may be multilobated especially extranodal such as primary bone DLBCL
Centroblastic MULTILOBATED
DLBCL NOS Immunoblastic Variant

- >90% cells immunoblastic
- Centrally located nucleolus
- Basophilic or amphophilic cytoplasm
- May have plasmacytoid cytoplasm
DLBCL NOS Anaplastic Variant

- Large round oval or polygonal cells with bizarre pleomorphic nuclei
- May resemble Hodgkin or RS cells
- May resemble ALCL
- May show sinusoidal and/or cohesive growth pattern
- May mimic undifferentiated carcinoma
- No related to T/NK cell ALCL or ALK-positive LBCL
DLBCL NOS Anaplastic Variant

CD20
Rare Variants Signet Ring Cell DLBCL

Cancer
52:1613
1983
DLBCL Marrow Involvement

- Marrow involvement 16%
  - Concordant (Large cell lymphoma) associated with poor outcome (5 year survival 10%)
  - Low grade lymphoma (discordant histology more common, similar outcome to negative marrow, but more frequent relapse, 5 year survival 62%)
  - 30% of patients with BM disease have circulating cells
DLBCL Concordant Marrow Involvement
BM Infiltration by Single Cells
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  - CD5+ DLBCL
  - Germinal centre B-cell like
  - Non-germinal centre B-cell like

- Germinal Center B-cell (GCB) with signature of germinal center B-cells (50% cases)
- Activated B-cell (ABC)
DLBCL GCB Signature

- BCL2
- Bcl-6
- CD10
DLBCL Activated signature (ABC)

• DLBCL with 'activated' gene profiles similar to those induced by in-vitro activation of peripheral blood B-cells by gene expression profiling have adverse prognosis

• Immunohistochemical markers include Mum-1 (IRF4), CD138
DLBCL 'Activated Signature'
Sub grouping DLBCL NOS by Immunophenotype (Hans Classifier)

Blood, 103:275-82, 2004
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- **Immunohistochemical subtypes**
  - CD5+ DLBC
CD5+ DLBCL

- Higher age distribution (mean 66 yrs)
- Female predominance
- Advanced disease
- B symptoms
- Aggressive clinical course
- Likely arise from the same progenitor cell as the mutated variant of CD5+ SLL/ČLL cell (Am J Clin Pathol 101:699-702, 2003)
- Arise de novo without prior history of CLL or MCL
- Distinguish from blastoid MCL by absent cyclin D1
- Blood 99:815-821, 2002
CD5+ DLBCL
Summary: DLBCL- Role of Immunohistochemistry

- Follicular signature characterized by CD10+, BCL6+/-
- Activated B-cell signature CD10-, BCL6-/+, BCL2+/- MUM1 (IRF4)+
- Expression of BCL2 protein by DLBCL implies a worse prognosis even in the rituximab era
- Activated phenotype MUM1+ correlates with worse prognosis and ABC signature
- Identify unique variants
  - plasmablastic lymphoma (lack Pax5, express CD138)
  - ALK+
  - CD5+ DLBCL
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  - Primary DLBCL of the CNS
  - Primary cutaneous DLBCL Leg type
  - EBV positive DLBCL of the elderly
- **Other Lymphomas of Large B-cells**
  - Primary mediastinal (thymic) LBCL
  - Intravascular LBCL
  - DLBCL associated with chronic inflammation
  - Lymphomatoid granulomatosis
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  - Large B-cell lymphoma arising in HHV8+ MCD
  - Primary Effusion Lymphoma
- **Borderline cases**
  - B-cell lymphomas unclassifiable
T-cell rich B-cell lymphoma

• Morphologic variant of DLBCL with minor component of large malignant B-cells in a T-cell/histiocyte rich background

• Large cells may be RS-like, centroblast/immunoblast like, or resemble L&H cells. May be confused with Hodgkin lymphoma particularly LPHL or lymphocyte rich Classical Hodgkin lymphoma
T-cell Rich B-cell Lymphoma
Clinical

• <10% DLBCL
• Age range 12-61 years
• Predominantly males (3-4 to 1)
• Mainly high stage III or IV
• Involves lymph nodes
• Bone marrow, liver, spleen involved at diagnosis in up to 60% of cases
• Refractory to therapy
T-cell Rich B-cell Lymphoma-Histology

- Diffuse effacement of nodal architecture
- Tumor cells evenly dispersed within clusters of bland histiocytes and small T-cells
- Eosinophils or plasma cells not present
- Large cells positive for B-cell markers, BCL6, negative for CD15, CD30, EBV
- Clonally rearranged IG genes carrying somatic mutations, resemble germinal center B-cells
TCRBCL Spleen
T-cell Rich B-cell Lymphoma

CD20

CD2

Bcl-6

Ki67
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Primary DLBCL of the CNS

- Primary intracerebral or intraocular lymphoma
- Lymphomas of the dura, intravascular lymphoma, secondary lymphomas, immunodeficiency lymphomas excluded
- <1% of NHL
- Most common in older males >60
- Multiple lesions in about 30%
- 25 year survival 40-75% (Blood 113:7, 2009)
Primary DLBCL of the CNS

- Tumor cells in perivascular space
- Mostly resemble centroblasts
- May be intermixed with reactive small lymphocytes, macrophages, active microglial cells, reactive astrocytes
- Necrosis frequent
- Positive for pan B-cell markers, BCL6, MUM1, negative for CD10, CD138
Primary DLBCL of the CNS
Primary DLBCL of the CNS: Just DLBCL or not?

• Poor prognosis compared with extracerebral DLBCL
• Histogenesis of the tumor cells?
• Transforming event?
• Role of the microenvironment?
• Blood 113:7-10, 2008
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Diffuse large B-cell lymphoma 'leg type'

- Mostly in elderly females, mostly but not always on the lower legs
- Sheets of centroblasts and immunoblasts with round cell morphology and frequent mitoses
- BCL-2+ (unlike cutaneous follicular lymphoma), BCL6+, Mum1/IRF4+, CD10-
- 50% five year survival
DLBCL Leg Type

[Images of medical samples and tissue sections]
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EBV+ DLBCL of the Elderly

• Previously called senile associated
• Defined as a clonal EBV+ large cell lymphoma
• WHO definition of elderly is >50, median age 70.
• No known cause for immunodeficiency or prior lymphoma. Related to senescence of the immune system.
• Rare cases in young patients but need to rule out an undiagnosed immunodeficiency
• Must exclude other EBV related LPD (lyg, mono, PEL etc).
• EBV in malignant cells, not bystanders. EBER+, LMP1+, EBNA2+
EBV+ DLBCL of the Elderly
Clinical Features:

• 70% extranodal including skin, lung, tonsil, stomach, 30% nodal alone
• 50% have high IPI and prognosis is inferior to EBV- DLBCL even if adjusted for age
• More refractory to initial therapy (CR 66%) and poor overall survival (2 years or less)
EBV+ DLBCL of the Elderly

- Histology varies from polymorphous to monomorphous
- Polymorphous cases similar to PTLD
- Geographical necrosis and RS-like cells common
- Variable component of reactive lymphocytes/histiocytes
- Most cases CD20+, CD79a+, MUM1+, CD10-, BCL6-, monoclonal
- H-RS cells EBV+ (LMP1 and EBNA2), CD20+, CD30+ 75%, CD15-
- Clonal by molecular genetics – may help distinguish from infectious mononucleosis of the elderly
EBV+ DLBCL of the Elderly
EBV+ DLBCL of the Elderly
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Primary Mediastinal (Thymic) LBCL

- DLBCL arising in the mediastinum from thymic B-cell
- 2-4% NHL
- Young adults (median 35 years), female predominance
- May present with SVC obstruction, dyspnea
- Often bulky disease >10cm
- Most have stage I/II disease
- Marrow involvement rare (3%)
- Aggressive, but more favorable prognosis than previously thought with intensive chemo +/- radiation therapy (CR rate 80%, plateau beyond 2 yrs.)
- Relapse in unusual sites (GIT, kidney, adrenal, CNS)
Primary Mediastinal DLBCL - Pathology

• Common histologic features but not required for diagnosis
  - Sheets of large B-cell with clear cytoplasm
  - Usually round or oval, can be multilobated
  - Prominent sclerosis (broad bands, compartmentalizing, interstitial)

• Distinct immunophenotype
  - Immunoglobulin negative,
  - CD30+ in 80%, usually weak, heterogeneous
  - CD23+ in 70% of cases
  - MAL+ in 70%

• Immunoglobulins rearranged with somatic hypermutations.

• Lack BCL2, BCL6, or MYC rearrangement
Primary Mediastinal DLBCL
Primary Mediastinal DLBCL
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Intravascular LBCL

- Synonymous terms: Angiotropic Large Cell lymphoma
- Multifocal, selective growth within lumina of capillaries
- Any organ affected, usually disseminated including marrow
- Lymph nodes usually uninvolved
Clinical features

• Average age 65 (range 34-85), slight male predominance.
• Present with weight loss, FUO, malaise and signs and symptoms related to occlusion of small vessels in various organs, most often the CNS and skin.
• Isolated cutaneous variant more in females
• Skin lesions include tender erythematous nodules, tumors, telangiectasia, cellulitis, lymphedema.
• Neurologic conditions include infarcts, dementia, polyneuropathy, myalgia.
Intravascular LBCL Phenotype

• 85-91% B-cells
• Rare T-cell and NK cell variants
• Bcl-2+, CD43+
• Variable CD5, CD10, MUM1.
• 20-25% express bcl-6
• Asian variant can be CD5+
Intravascular LBCL

Large cells with prominent nucleoli
May have fibrin thrombi, hemorrhage and necrosis
Bone marrow Intravascular LBCL
**DLBCL Variants, Subgroups, and Subtypes /Entities (WHO 2008)**

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Plasmablastic Lymphoma

- Diffuse proliferation of large cells which resemble B-immunoblasts or plasmablasts, and have the phenotype of plasma cells.
- First described in the oral cavity but may occur in other, predominantly extranodal sites including nasal sinuses, skin, soft tissue, GIT
- Usually males, median age 40
- Aggressive clinical course.
- Highest association with HIV but can occur with other immunodeficiencies including PTLD and the elderly. Some cases no history of immunodeficiency.
- Cases not associated with HIV more common in lymph nodes. Most are stage IV at diagnosis.
Plasmablastic lymphoma Phenotype

- Majority are EBV+, KSHV-/+.
- Frequent MYC/IgH rearrangements
- Immunophenotype
  - Weak CD45+, CD20-/+; Pax 5-/+.
  - CD79a+ in 50-85% cases.
  - CD38+, CD138+, MUM1+, EMA+.
Plasmablastic lymphoma
Plasmablastic Lymphoma Subtypes

- **Oral mucosa type**
  - Minimal plasmacytic Differentiation
  - Often associated with HIV
  - Usually extranodal, may involve lymph nodes

- **PBL with plasmacytic Differentiation**
  - Plasmablastic appearance
  - May be indistinguishable from plasmacytoma/myeloma, clinical history important

- **Differential** includes HHV-8 Associated lymphomas (PEL, extracavitary PEL, Multicentric Castleman’s) and plasmablastic myeloma). If HHV-8+ considered form of PEL not plasmablastic lymphoma.
Plasmablastic Lymphoma Oral Cavity Type
Plasmablastic lymphoma
Plasmacytic

Differential from extramedullary plasmablastic myeloma requires clinical history
EBV+ in most PBL, only occasionally in myeloma
Myeloma more often CD56+, cyclinD1+
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  - ALK positive LBCL
  - Plasmablastic lymphoma
  - Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
  - Primary effusion lymphoma
- Borderline cases
ALK+ Diffuse Large B-cell Lymphoma

- ALK-positive DLBCL often have immunoblastic or plasmablastic morphology and involve subcapsular sinuses of lymph nodes.
- M:F 3:1, occurs at all ages median 36yrs
- Immunocompetent EBV-, KSHV-
- CD30-, CD57+, EMA+, CD138+, CD79a+/-, CD20-, cIgA+
- Present with generalized lymphadenopathy and advanced stage. Often extranodal: skin, bone, brain
- 3 year survival 30%
ALK+ DLBCL
ALK+ DLBCL

- Most cases show t(2;17)(p23;q23) with fusion of ALK and clathrin gene leading to cytoplasmic granular staining for ALK
- Rare cases show t(2;5) with NPM/ALK nuclear and cytoplasmic staining
- Must distinguish from systemic ALCL which are T/NK cell neoplasms
- ?ALK activation in B-cells turns on the plasma cell differentiation program
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Lymphomatoid granulomatosis

- Angiocentric angiodestructive lymphoproliferative disease involving extranodal sites, composed of EBV+ B-cells admixed with reactive T-cells which usually predominate
- More common in adult males
- Prototype: Pulmonary involvement (bilateral peripheral lung nodules, solitary mass, or diffuse infiltrate)
- Other sites: skin, CNS, kidney, liver
- Importance of recognition: Early lesions Grade 1 or 2 may wax and wane respond to interferon alpha. Grade 3 aggressive regimens with rituximab
Lymphomatoid Granulomatosis

• Pulmonary nodules vary in size, often bilateral
• Histologic triad:
  - Atypical polymorphous lymphoid infiltrate often with a granuloma-like appearance
  - Angiocentric and angiodestructive
  - Prominent geographic necrosis
• Confirmation of diagnosis:
  - CD20+ large cells, CD3+ reactive small cells
  - ISH for EBER and immunostain for EBV LMP1
  - Most Grade 2/3 cases have Ig gene rearrangements
Lymphomatoid Granulomatosis Grading

Grade I
Polymorphous
No atypia
Sparse EBV+ cells

Grade 2
Polymorphous
Scattered large EBV+ cells 5-20

Grade 3
Large cells form aggregates
>50 EBV+ cells/HPF

Worsening prognosis with increased large EBV+ cells, increasing necrosis, clusters of large cells
Lymphomatoid Granulomatosis
Immunohistochemistry

CD20

EBV EBER

EBV LMP
DLBCL Variants, Subgroups, and Subtypes /Entities (WHO 2008)

- Diffuse Large B-cell Lymphoma NOS
- Diffuse Large B-cell Lymphoma Subtypes
- Other Lymphomas of Large B-cells
  - Primary mediastinal (thymic) large B-cell lymphoma
  - Intravascular large B-cell lymphoma
  - DLBCL associated with chronic inflammation
  - Lymphomatoid granulomatosis
  - ALK positive LBCL
  - Plasmablastic lymphoma
  - Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
  - Primary effusion lymphoma
- Borderline cases
Primary Effusion Lymphoma

- Serous effusion in the absence of a tumor mass
- Rarely present with or develop solid tumors
- Express CD45, negative for B-cell markers despite immunoglobulin gene rearrangements.
- Express activation antigens CD30, CD38, CD138
- EBER+, EBV LMP-, HHV8 demonstrated by LANA stain.
Primary Effusion Lymphoma (PEL)

HHV8 LANA
Summary DLBCL

• Becoming more complicated – many subcategories in WHO-2008
• Heterogeneous in morphology and response to therapy
• Still limited treatment options (R-CHOP) but worth identifying subtypes with more aggressive clinical course
• New therapeutic options, EPOCH-R, BMT, CNS prophylaxis for aggressive subtypes.
Burkitt Lymphoma

- BL 1%
- PMLB 3%
- DLBCL 37%
Burkitt lymphoma

- Monomorphic medium sized transformed B-cells with round nuclei, clumped chromatin, basophilic cytoplasm, squared off cell borders, cytoplasmic vacuoles, medium sized paracentral nucleoli, starry sky pattern
- Translocation involving MYC characteristic but not specific or always identified
- No single parameter is gold standard; morphology, genetic immunophenotype, expression profiles
Burkitt Lymphoma Clinical Features

• 1-2% in USA
• 30-50% childhood lymphomas
• Median age adult 30 yrs
• Majority present as abdominal mass with ileocecal and other organ involvement. May present as acute leukemia
• Bone marrow involvement at presentation uncommon with exception of HIV
• Usually treated with aggressive therapy (Hyper CVAD or related regimen plus CNS prophylaxis)
BURKITT LYMPHOMA - Clinical Variants

- **Endemic**
  - Equatorial Africa
  - Strong association with EBV 95%
  - Commonly in children, affects jaws, gonads, kidneys

- **Sporadic**
  - EBV in about 40%
  - Children and young adults
  - Involves terminal ileum and Waldeyer’s ring
  - Marrow involvement more common than in the endemic form

- **AIDS-associated**
  - Associated with HIV with relatively high CD4 counts
  - More frequent nodal and BM localization
Burkitt Lymphoma Morphology
BL Marrow/Peripheral blood
Burkitt lymphoma phenotype/genotype

- Germinal centre phenotype expressing IgM+, CD10+, BCL2-, TdT-, BCL6+, Ki67 100%
- Few reactive CD3+ T-cells
- IgM+, Immunoglobulin genes hypermutated but no class switch
- Documentation of MYC translocation highly desirable but no essential for diagnosis
- 30% p53 positive
Phenotype Burkitt Lymphoma

- **CD20**
- **Ki-67**
- **TCL1**
Diagnosis of Burkitt lymphoma usually easy but sometimes difficult because:

- Rarely BL may be negative for BCL-6; BCL6 gets down regulated by EBV
- About 20% BL may be BCL2 weakly positive
- Aberrant phenotypes occur including CD4+ BL
- BL may be positive for MUM1 (up to 50%)
- May get pleomorphism following therapy
- May have overlapping features with DLBCL
MYC translocations in Burkitt Lymphoma

- t(8;14) in 90%
- t(8;2) or t(8;22) in 10-15%
- Occasionally other translocation partners may be missed with break apart probes so appear MYC negative in about 10% of cases.
- Helpful clue: Karyotype simple in BL, few additional abnormalities other than MYC (cf. MYC+ DLBCL)
**MYC break apart Probe for Interphase FISH**

![Diagram of MYC region with break apart probe annotations]

LSI MYC Dual Color, Break Apart

![Micrographs showing fluorescence in situ hybridization (FISH) results]
Atypical BL (WHO 2001)

- WHO 2001 defined atypical BL cells with large central single nucleoli and more pronounced variation in size and shape
- Category eliminated for WHO 2008
AIDS-Associated Burkitt Lymphoma

- EBV association 40%
- 30% of NHL in AIDS
- Young adults with relatively high CD4+ counts
- Lymph nodes as well as extranodal sites, marrow, GIT
- Often has an 'atypical' or plasmacytoid appearance
Overlapping features BL vs DLBCL

- DBCL proliferation rate can approach 100% with frequent apoptotic bodies and/or starry sky macrophages.
- BL may have admixed larger cells, and DLBCL may have medium-sized cells.
- C-MYC translocation is hallmark of BL but may occur in DLBCL.
Burkitt vs DLBCL

- Using gene expression profiling as the 'gold standard' expert pathologists misdiagnosed BL as DLBCL or High Grade B-cell lymphoma unclassifiable.

Aggressive B-cell lymphomas take home messages:

• Usually an easy diagnosis, if it looks like DLBCL or BL it probably is.
• Atypical BL or Burkitt-like lymphoma no longer used by WHO 2008
• Remember to exclude “look alikes” including carcinoma, granulocytic sarcoma
• Don’t be confused by phenotypic heterogeneity
• Use molecular studies as adjuncts to diagnosis but trust the microscope
• Work with your oncologists, clinical information is important
• You can help clinicians and patients by pointing the way to appropriate therapy for aggressive subtypes