Diffuse Large B-Cell Lymphoma: Variants & Subtypes

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Subclassifying DLBCL

"An Entity in Search of a Meaningful Classification"

Subclassifying DLBCL

A glimpse of the future: Molecular classification

Subclassifying DLBCL

Back to the present:
Separating special subtypes from DLBCL, NOS

- DLBCL, NOS (most common)
  - Morphologic variants (centroblastic, immunoblastic, anaplastic)*
- Specific clinicopathologic subtypes (thought to differ biologically from DLBCL, NOS), specified by:
  - Site of disease (e.g., 1° mediastinal, 1° CNS, intravascular)
  - Morphology (e.g., T-cell/histiocyte-rich large B-cell lymphoma)
  - Phenotype (e.g., ALK+ large B-cell lymphoma)
  - Virus association (e.g., EBV+ DLBCL of the elderly)
  - Genotype (e.g., MYC+/BCL2+ DLBCL)

*Reporting optional per 2008 WHO Classification
### DLBCL, clinicopathologic subtypes

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- LBCL arising in multicentric Castleman’s disease

### “Unauthorized” DLBCL Subtypes

- Primary DLBCL of bone
- *De novo* CD5+ DLBCL
- $MYC^+\text{/}BCL2^+$ DLBCL
- Others
Mantle cell lymphoma, pleomorphic variant
Grade 3B follicular lymphoma
"One should think twice and thrice before rendering a diagnosis of DLBCL in a patient younger than 20 years. Infectious mononucleosis in particular has to be suspected when there are many admixed large T-cells and Waldeyer’s ring is involved."

- ACL Chan & JKC Chan, 2011

Diffuse large B-cell lymphoma, in Hematopathology (Saunders/Elsevier)

The “Panel o’ Five”
(for probable DLBCL cases)

- CD20
- CD21*
- CD5
- BCL-1 (cyclin D1)
- EBV-ISH

*Particularly in needle core biopsies

DLBCL Diagnosis

**Three simple steps...**

1. Consider & exclude DLBCL mimics
2. Consider specific DLBCL subtypes
3. If no fit with specific DLBCL subtypes, place in category of DLBCL, NOS
Diffuse large B-cell lymphoma

**Morphologic Variants**

**Centroblastic:**
- Most cells are centroblasts
- Nuclei usually round to oval, but may be irregular or lobated
- Up to 90% can be immunoblasts!
- Most common variant

**Immunoblastic:**
- >90% cells immunoblasts
- Centroblasts ≤10%
- May show plasmacytoid differentiation (mimicking plasmablastic lymphoma)
Diffuse large B-cell lymphoma

**Morphologic Variants**

**Anaplastic variant:**
- Very large cells with pleomorphic nuclei
- May resemble RS-cells of classical HL
- May grow in cohesive sheets in LN sinuses, mimicking metastatic carcinoma or ALCL
- Roughly half of cases CD30+
- ALK- t(2;5)- thus unrelated to ALCL
- Behavior & response to therapy similar to other DLBCLs
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**Primary mediastinal (thymic) LBCL**

- Median age at presentation 37 years
- Female predominance (2:1)
- Generally present with large anterior MS mass (bulk of tumor in anterior MS by definition)
- Most cases low-stage at presentation, but disseminatation (1/3 cases) often involves extranodal sites, such as kidney, liver, skin, brain
- Morphology often resembles DLBCL, NOS, but fine "compartmentalizing" fibrosis often present
- Cells usually CD30+, sometimes CD15+, but strong expression pan-B-cell markers with exception of sIg
- Derived from thymic medullary B-cells? (MAL+)
- Gene expression profile resembles CHL
### B-cell antigen expression in CHL

**Table 1** Total (N* = 323)

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<td>64</td>
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</tbody>
</table>

++ intense in most cells  + weak & focal  - completely absent

García-Cosío et al. Mod Pathol 17: 1531; 2004

### Primary DLBCL of the CNS

- Rare NHL (<1%), median age 60 years at presentation
- Must exclude more common secondary CNS involvement; WHO definition also excludes dural & intravascular tumors and those arising in immunodeficient patients (most EBV-)
- Large B-cells typically resemble centroblasts, diffusely infiltrates brain parenchyma and perivascular spaces
- Majority MUM1+ BCL6+ but CD10-; most non-GCB by IHC
- GEP data suggests possible distinctive “CNS signature”
- Spread outside CNS uncommon
- Prognosis generally poor, but some long term survivors

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**Primary cutaneous DLBCL, leg type**

- Identified by epidemiologic studies that found location on leg to be poor prognostic factor for cutaneous B-cell lymphomas
- Primarily elderly women, median age 76 years
- Present as dermal nodules or plaques (must exclude secondary dermal involvement clinically)
- Dermal infiltrates of centroblasts and/or immunoblasts, nuclear contours often quite round; no spread into epidermis
- If numerous centrocytes present, is most likely primary cutaneous follicle center (follicular) lymphoma
- Typically BCL2+ BCL6+ MUM1+ CD10- (most 1° cutaneous FCL are BCL2- or weak), most ABC type by GEP
- Most on lower leg, but presents at other sites in 10-15%
- Aggressive with only 41% 5-year survival
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**Intravascular large BCL**

- Very rare variant of DLBCL, typically of older adults (median age 67 years)
- Large B-cells present exclusively in lumens of blood vessels, without formation of mass lesion
- Can involve one or more organs, most common CNS, skin, lung, kidney, adrenal gland, liver
- Clinical manifestations highly variable
- Very poor prognosis, likely reflecting frequent delay in diagnosis (often not made till autopsy)
- Asian variant with associated hemophagocytic syndrome reported from Japan
- Most non-GCB type, some CD5+
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**T-cell/histiocyte-rich LBCL**

- Uncommon subtype of DLBCL (<10%)
- Males, mean age 46 years (younger than NOS), who typically present with B symptoms & high stage disease (liver, spleen, BM often involved at diagnosis)
- Large B-cells <10%, do not form large clusters or sheets; may resemble LP cells of NLPHL\(^1\) or RS cells of CHL\(^2\)
- Small T-cells and/or histiocytes predominate in background, small B-cells rare to absent (0.7x large cells)
- Neoplastic large B-cells CD30+ in up to 40% of cases
- GEP shows “host response” pattern
- Often refractory to therapy

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\(^1\)True NLPHL will have focal nodules (by H&E or CD21).  
\(^2\)True CHL will have CHL phenotype; if doesn’t, but cells RS-like and EBV+, consider diagnosis of EBV+ DLBCL of elderly.
It's a non-Hodgkin lymphoma you idiot...
**Plasmablastic Lymphoma**

- Aggressive solid tumor of malignant large B-cells
- Cells resemble plasmablasts or immunoblasts
- CD20 expression generally negative but weak staining (<25% of cells) in some cases
- Often presents in oral cavity, but can also involve other mainly extranodal sites (not as effusions)
- Patients mainly HIV+, other immunocompromised
- Most tumors EBV+
- HHV-8 (KSHV) negative (by definition?)
- Very poor prognosis, median survival 6-7 months

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Diffuse Large B-cell Lymphomas With Plasmablastic Differentiation Represent a Heterogeneous Group of Disease Entities

Lluis Colomo, MD,* Florence Lioung, MD,† Susana Rives, MD,* Stefania Pittaluga, MD,‡ Antonio Martínez, MD,* Armando López-Guillermo, MD,* Jesús Ojanguren, MD,*‡ Vicente Romaguera, MD,* Julia S. Jaffe, MD,* and Elisa Campo, MD*†

Abstract: Plasmablastic lymphoma was initially described as a variant of diffuse large B-cell lymphoma (DLBCL) involving the oral cavity of HIV+ patients and characterized by immunoblastic morphology and a plasma cell phenotype. However, other lymphomas may exhibit similar morphology and immunophenotypic features. To determine the significance of plasmablastic differentiation in DLBCL and examine the heterogeneity of lymphomas with these characteristics, we examined 90 DLBCLs with known CD10, CD20, BCL6, and an immunophenotype indicative of terminal B-cell differentiation (CD45+CD20+CD10-EMA-positive). We were able to define several distinct subgroups. Twenty-three tumors were classified as DLBCL: HHV-8 was examined in 10 additional cases, and was negative in all. In conclusion, DLBCLs with plasmablastic differentiation are a heterogeneous group of neoplasms with different clinicopathological characteristics that may correspond to different entities.

Key Words: large cell lymphoma, plasmablastic, HIV, HHV-8, EBV, immunohistochemistry.

Primary Effusion Lymphoma

- Malignant effusion without associated mass lesion
- Immunocompromised patients, mainly late-stage AIDS with low CD4 counts and history of KS
- Cells generally resemble centroblasts or immunoblasts, but can be pleomorphic
- Cells infected by HHV-8 (KSHV) and usually EBV
- B-lineage with plasma cell phenotype, but unlike PBL usually CD30+ CD45+
- Extremely poor prognosis
- Extracavitary PEL?
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**ALK+ large B-cell lymphoma**

- Very rare form of DLBCL (<40 cases reported)
- Males > females (3:1), wide age range pediatric → adult
- Typically presents in lymph nodes, but some extranodal
- Most patients present with advanced stage disease
- Tumor cells resemble immunoblasts or plasmablasts, but can be RS-like, and typically infiltrate lymph node sinuses
- Has CD20- Pax5- Oct2+ BOB.1+ plasma cell phenotype (overlap with plasmablastic lymphoma)
- ALK staining typically cytoplasmic & granular, and due to t(2;17) linking ALK with CLTC gene.
- Median surv. 11 mo. (some pediatric long-term survivors)
**EBV+ DLBCL of the elderly**

- Newly recognized aggressive form of DLBCL thought to be related to senescence of immune system
- Patients >50 years, no history of immunodeficiency
- Involves lymph nodes or extranodal sites
- RS-like cells present, sometimes in polymorphous background, resembling CHL or TCHRLBCL
- Variable CD30+, but usually strong CD20 & Oct2
- Rare cases may lack CD20 (overlap with PBL)
- Very poor prognosis (<50% 2-year survival), with exception of polymorphous type forming ulcers in skin or oropharynx ("EBV+ mucocutaneous ulcer")
- WHO excludes other defined EBV+ DLBCLs (PEL, PBL, LYG, DLBCL associated with CI)

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Lymphomatoid granulomatosis

- Rare EBV+ angioinvasive & angiodestructive B-cell LPD
- Most patients adults (M:F 2:1), but can occur even in children
- Almost always presents with pulmonary involvement, but can also involve CNS, kidney, liver, and skin; LN & spleen involvement rare
- Destruction of blood vessels may cause focal necrosis
- Background cells polymorphous mixture of small lymphocytes (mainly T-cells), histiocytes, and plasma cells; true granulomas rare
  - Grade 1: large B-cells rare to absent, EBV+ cells <5/HPF
  - Grade 2: large B-cells form small clusters, EBV+ cells 5-20/HPF
  - Grade 3: large B-cells HRS-like, form large clusters, EBV+ cells >50/HPF
- Patients often have evidence of immunodeficiency (PTLD-like?)
- Grade 3 usually clonal, aggressive, and considered a variant of DLBCL (though some may show spontaneous remission)
- Grades 1 & 2 more variable course, often respond to interferon rx
EBV-LMP1
**EBV-LMP1**

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**DLBCL associated with chronic inflammation**
- EBV+ DLBCL arising setting of long-standing chronic inflammation within a confined space
- Related to “localized immunodeficiency” due to build up of immunosuppressive cytokotkines (e.g., IL-10)
- Prototype is pyothorax-associated lymphoma (PAL) in patients with chronic pyothorax following therapeutic pneumothorax for tuberculosis
- Long latency period (20-64 years)
- Tumor grows along tissue planes in pleura, joints, soft tissues, sometimes without discrete mass
- May have resemble CD20+ DLBCL, NOS or PBL with plasma cell phenotype; some express CD3
- Non-GCB & aggressive (5-year survival 20-35%)

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Aozasa J Clin Exp Hematopathol 46:5; 2006
**LBCL arising in HHV8+ multicentric Castleman disease**

- Arises in lymph nodes or spleen of patients with HHV8+ multicentric Castleman disease (most patients HIV+)
- HHV-8+ large B-cells (termed plasmablasts but many resemble immunoblasts) have mature B-cell phenotype (CD20+), are EBV-, & express monotypic λ light chains
- These HHV-8+ large B-cells can form:
  - Expanded mantle zones around germinal centers ("plasmablastic CD") → λ monotypic but polyclonal
  - Small clusters, which may replace germinal centers ("plasmablastic microlymphoma") → λ monotypic but polyclonal
  - Sheets of cells that efface architecture ("frank plasmablastic lymphoma") → λ monotypic & monoclonal
- Only the latter is a true aggressive DLBCL
- *Unrelated* to plasmablastic lymphoma of oral mucosa type (CD20- EBV+ HHV8-)

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**Diffuse Large B-Cell Lymphoma**

*Prognostic Markers*

- CD10
- BCL6
- MUM1

“Cell of origin” per Hans et al.