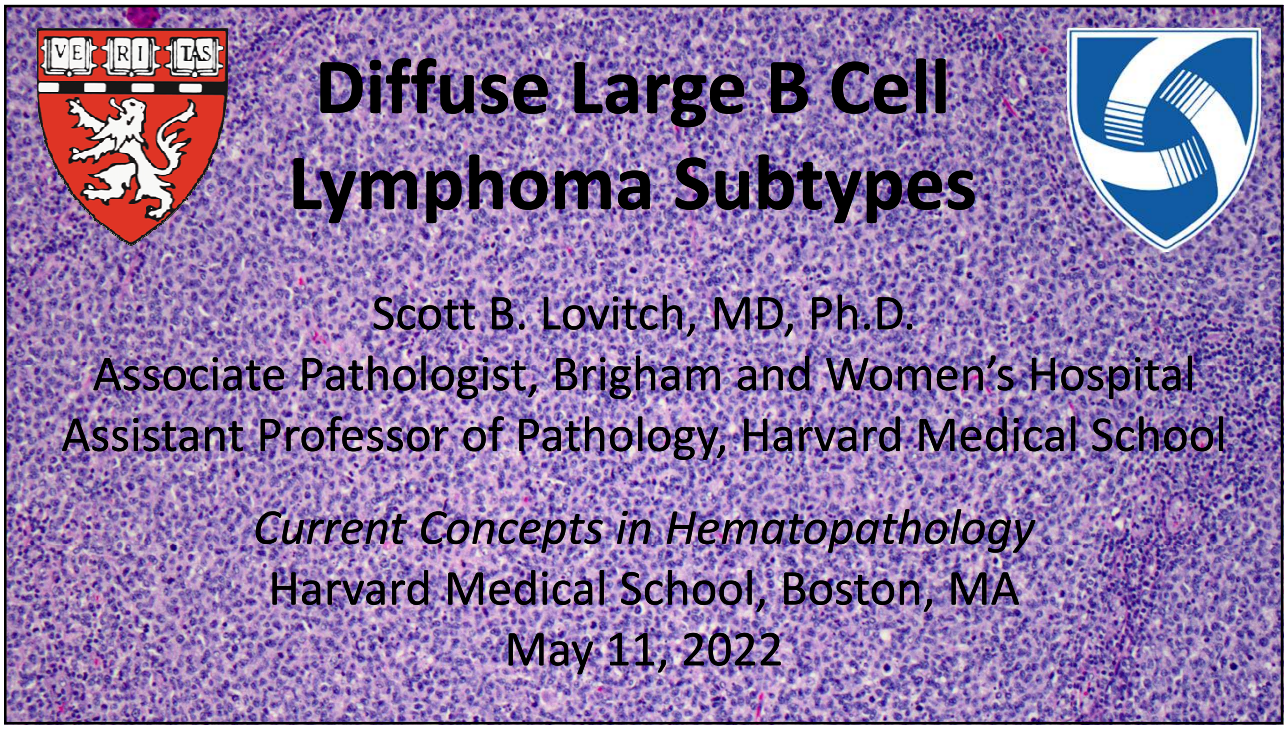

Diffuse Large B Cell Lymphoma Subtypes

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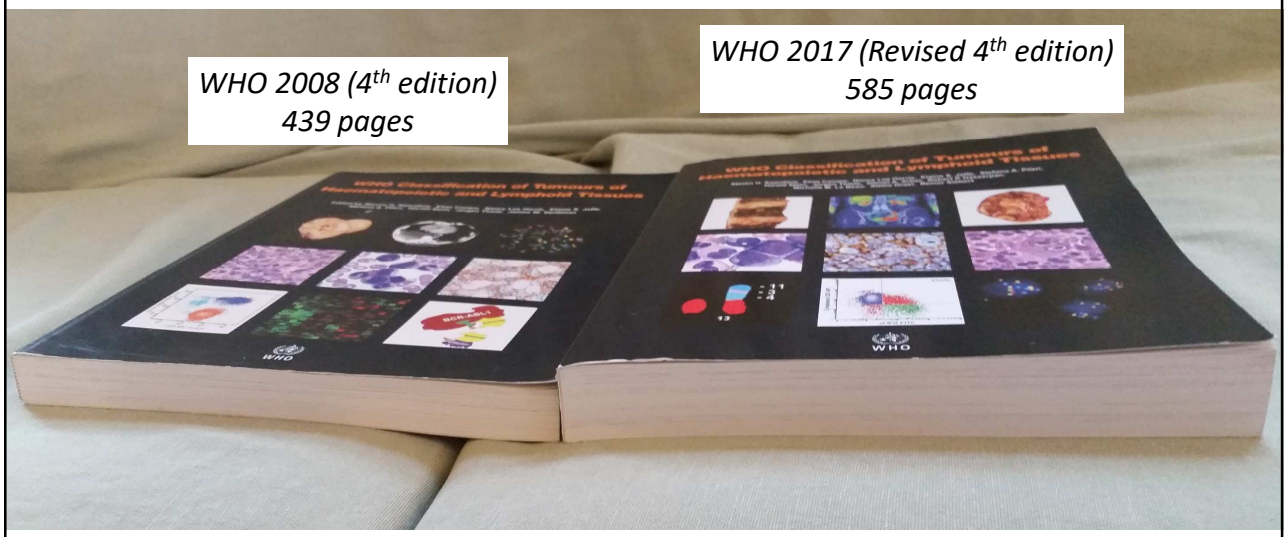
Current Concepts in Hematopathology
Harvard Medical School, Boston, MA
May 11, 2022

Disclosure

I have no financial relationship with any commercial entity producing healthcare (or healthcare education) related products and/or services.



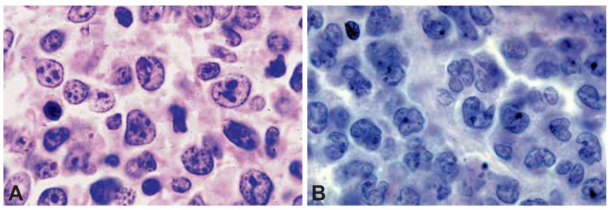
Changes to DLBCL classification in WHO revised 4th ed.

- Cell-of-origin subclassification now *required*
  - Germinal center B cell-type (GCB) vs. activated B-cell/non-germinal center B cell type (ABC/non-GCB)
  - Can use IHC or gene expression profiling (no specific algorithm required)
  - Impact on therapy
- Role of MYC and BCL-2 coexpression (separate from gene rearrangement)
  - Designation of "double expressor" status – new prognostic marker
- EBV+ DLBCL ~~*of the elderly*~~ (no longer age-dependent)
  - Recognition that this entity may occur in younger patients
- New provisional variants
  - Large B cell lymphoma with IRF4 rearrangement
  - EBV+ mucocutaneous ulcer

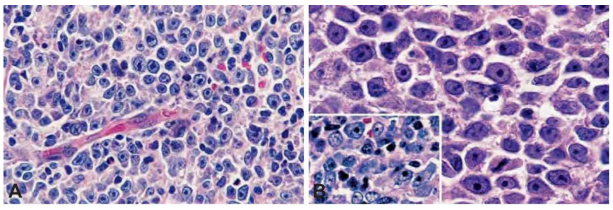
What hasn't changed:

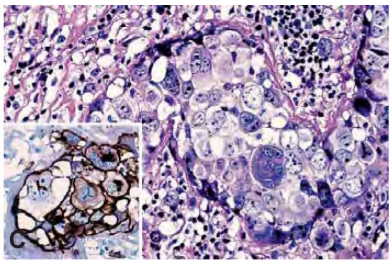
Morphologic variants

Centroblastic



Immunoblastic



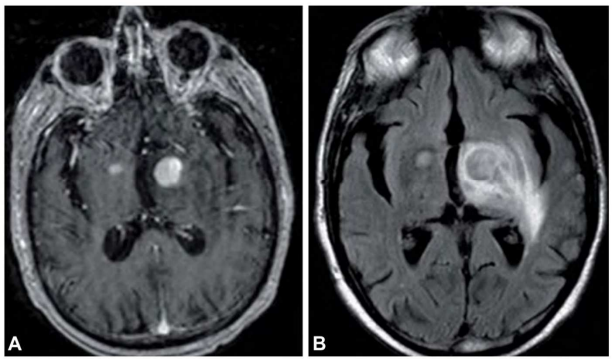


Anaplastic (inset: CD20 IHC)

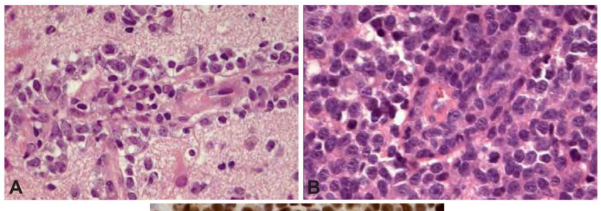
What hasn't changed:

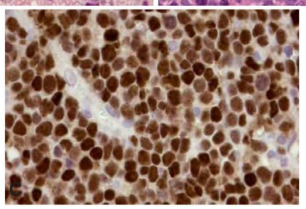
"Location-specific" variants

Primary central nervous system lymphoma (PCNSL)



T1 weighted imaging (A) and FLAIR sequence (B) post-gadolinium injection



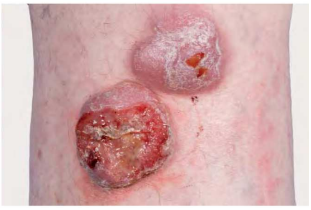


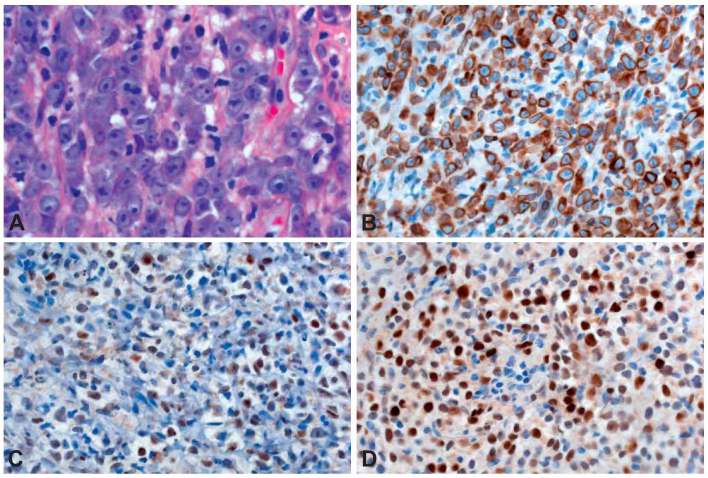
H&E (A, B) and IHC for IRF4/MUM-1 (C)

What hasn't changed:

"Location-specific" variants

Primary cutaneous DLBCL, leg type





Left: Gross image (10-15% at sites other than leg)

Right: H&E (A) and IHC for BCL-2 (B), BCL-6 (C), and IRF-4/MUM-1 (D)

Cell-of-origin classification in DLBCL:

Background

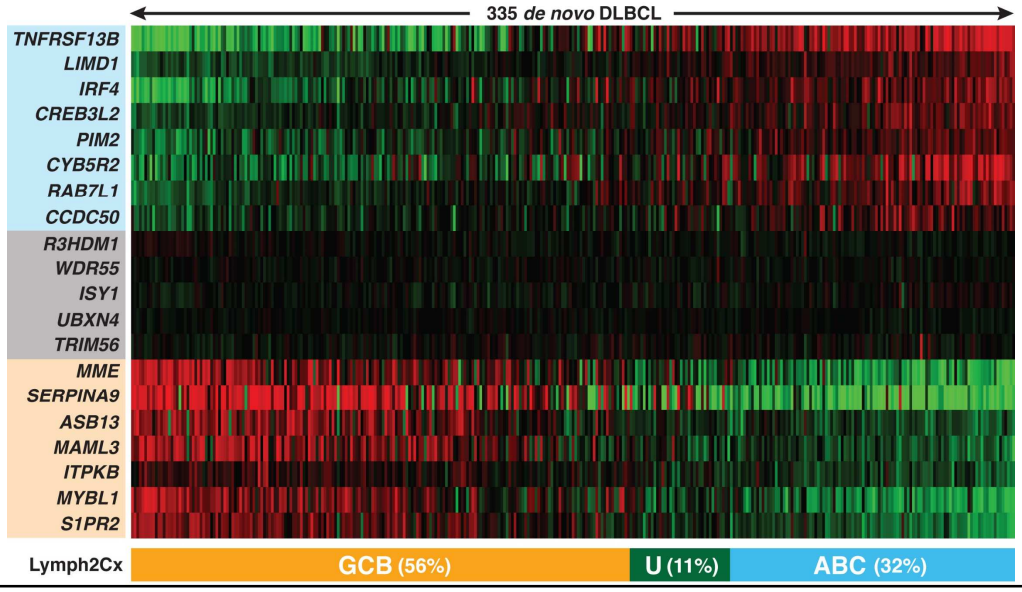
- WHO 2008 recognized molecular subgroups of DLBCL based on gene expression profiling (GEP)*:* Germinal center B cell-like (GCB), activated B cell-like (non-GCB/ABC), and unclassifiable

- However, subclassification was considered *optional* because:
  - GEP not routinely available
  - IHC didn't "exactly correlate" with molecular categories
  - Didn't affect therapy

- Better understanding of molecular pathogenesis of GCB and non-GCB subtypes, and emerging impact on selection of treatment, led WHO to *require* cell-of-origin classification (as GCB or non-GCB) in 2016 revision

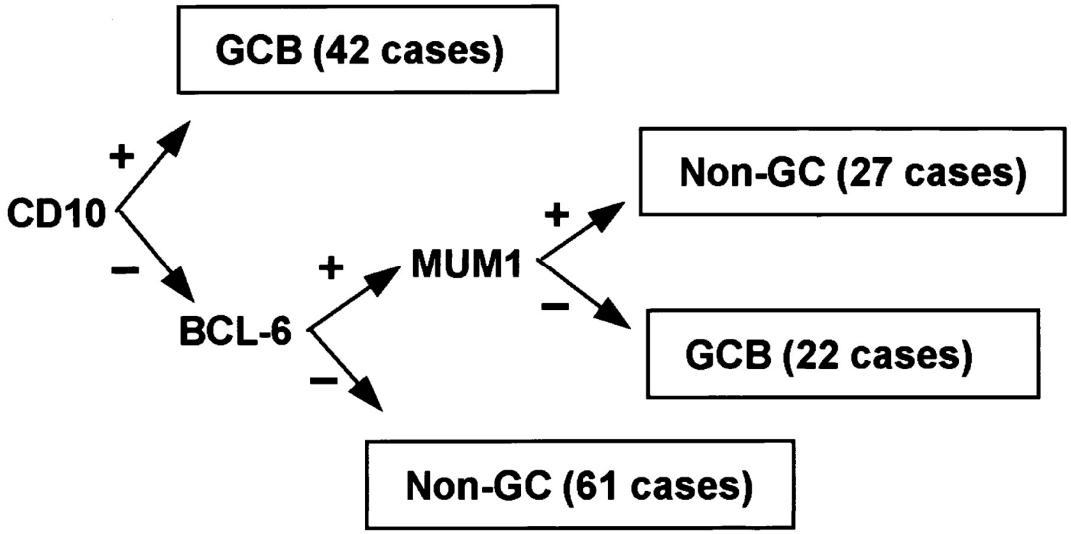
Cell-of-origin classification in DLBCL

Assessment by gene expression profiling



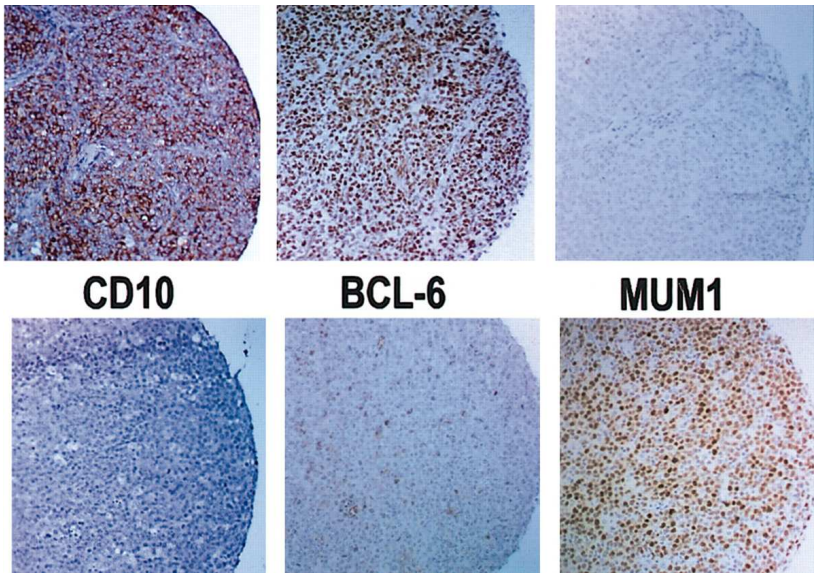
Cell-of-origin classification in DLBCL

Assessment by IHC: Hans algorithm



Cell-of-origin classification in DLBCL

Assessment by IHC: Hans algorithm

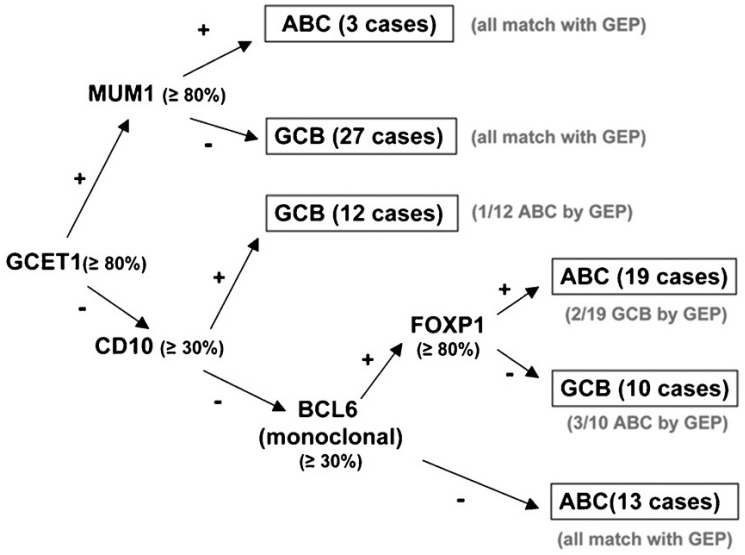


Germinal center B-cell type (GCB)

Non-germinal center B-cell/activated B-cell type (non-GCB/ABC)

Cell-of-origin classification in DLBCL

Assessment by IHC: Choi algorithm



- Slightly better performance than Hans algorithm (93% concordance with GEP vs. 86%)
- Application limited by lack of clinically validated, commercially available antibodies to GCET1 and Foxp1

Cell-of-origin classification in DLBCL

Assessment by IHC: "Tally" algorithm (Meyer et al)

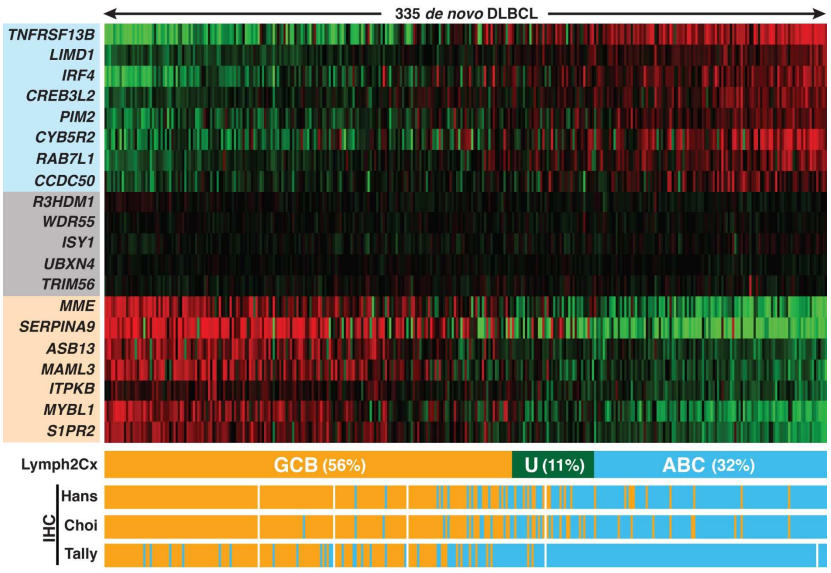
GCB	ABC	Score
CD10 (+ or -)	Mum1 (+ or -)	GCB > ABC
GCET1 (+ or -)	FoxP1 (+ or -)	or
Score (0, 1, 2)	Score (0, 1, 2)	ABC > GCB

If GCB Score = ABC Score:
- LMO2 ≥ 30% → GCB
- LMO2 < 30% → ABC

Similar to Choi algorithm, with addition of LMO2 as additional classifier

Cell-of-origin classification in DLBCL:

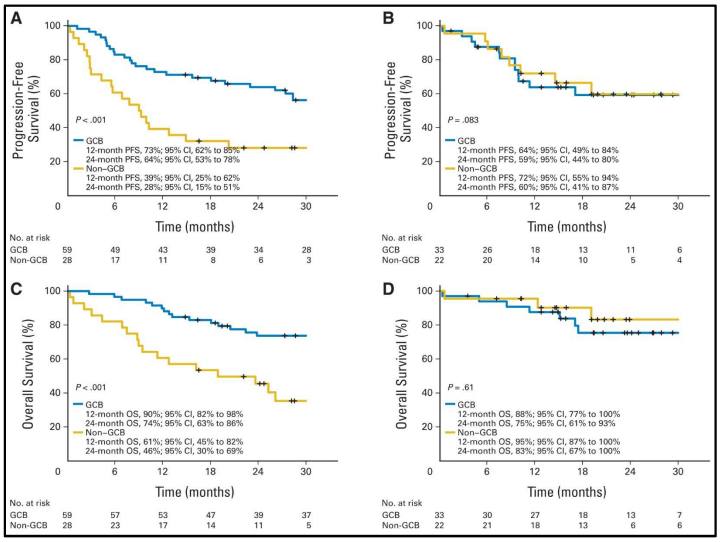
Comparison of IHC vs. GEP



Cases classified as GCB or ABC by gene expression profiling show strong concordance with IHC, regardless of algorithm used

Cell-of-origin classification in DLBCL:

Why it matters



Progression-free and overall survival for patients treated with standard R-CHOP chemotherapy (A and C) and with R-CHOP + lenalidomide (R2CHOP; B and D)

Addition of lenalidomide improves survival in non-GCB but not GCB-type DLBCL

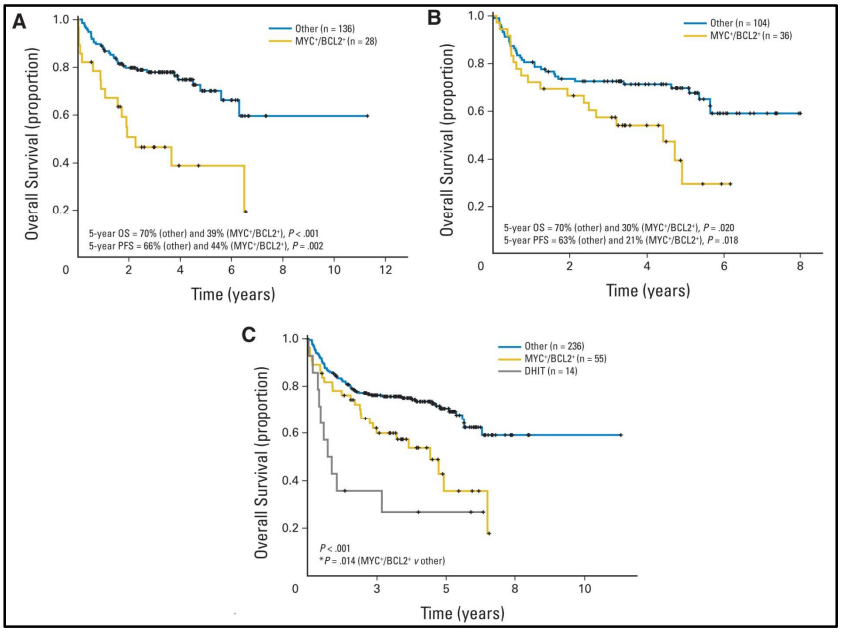
MYC/BCL-2 double-expressor DLBCL

Background

- WHO 2008 recognized LBCLs with MYC and BCL-2 translocations ("**double-hit lymphoma**" under category of "B cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma"
  - ➢ Reclassified in WHO 2016 as "High grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements"
  - ➢ Dr. Sohani will discuss these in an upcoming session

- Increased recognition that MYC and BCL-2 protein coexpression is an independent prognostic factor (irrespective of genetic status) – so-called "**double-expressor lymphoma**"
  - ➢ Worse outcome than non-double-expressor DLBCL, NOS
  - ➢ But not as aggressive as (genetic) double-hit lymphoma

MYC/BCL-2 double-expressor DLBCL

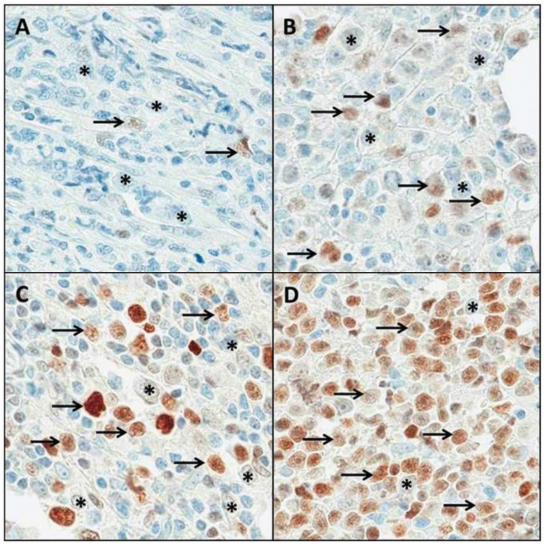


MYC/BCL-2 double-expressor DLBCL has worse progression-free survival (A) and overall survival (B) on R-CHOP chemotherapy

However, still not as bad as true (i.e., genetic) double-hit lymphoma (C)

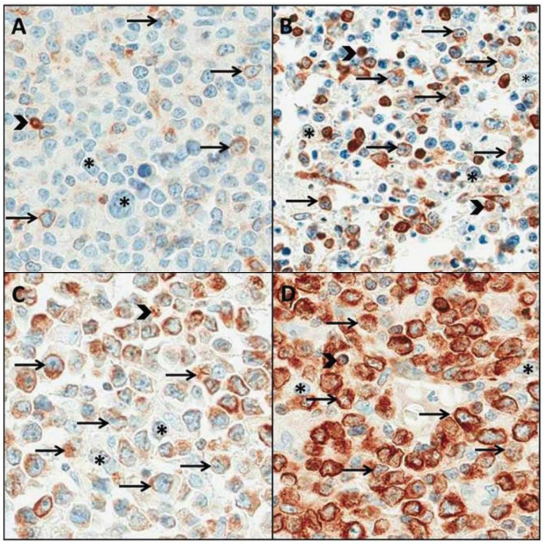
MYC/BCL-2 double-expressor DLBCL

MYC IHC (Y69; Ventana)



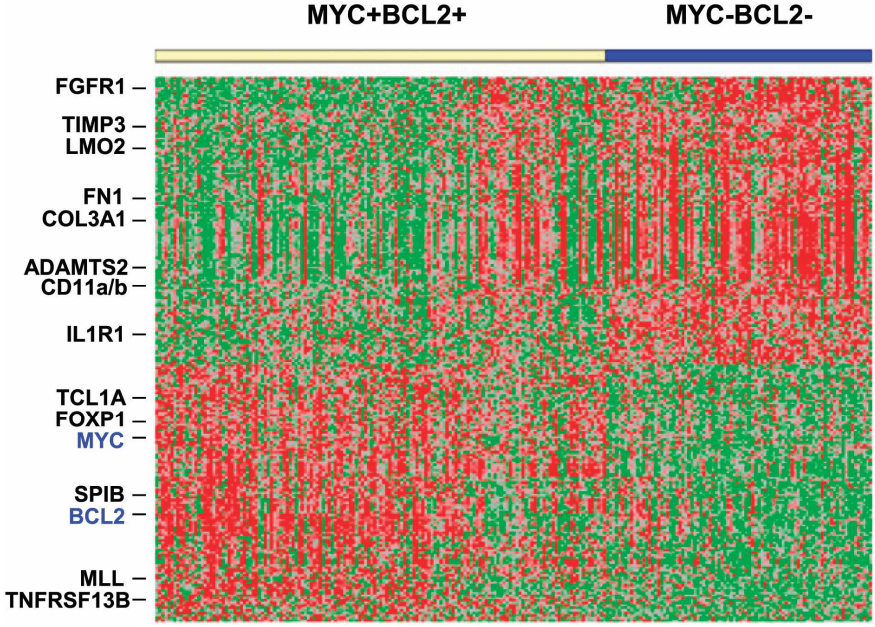
A-D: <10%; 20%; 40%; 80%

BCL-2 IHC (SP66; Ventana)



A-D: 10%; 40%; 70%; 90%

MYC/BCL-2 double-expressor DLBCL



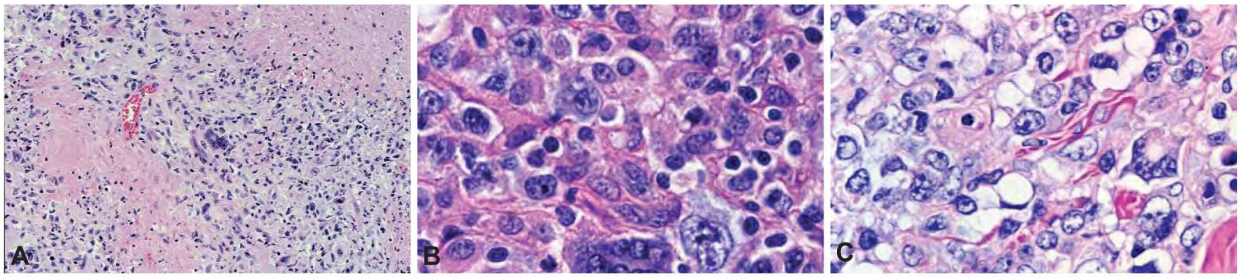
MYC/BCL-2 double-expressor DLBCL has a unique gene expression profile (downregulation of cell adhesion and cytoskeletal organization, upregulation of cell proliferation and cell metabolism)

EBV+ DLBCL ~~of the elderly~~

Background

- WHO 2008 recognized "EBV-positive DLBCL of the elderly" as a provisional entity
  - Occurs in apparently immunocompetent patients ≥50 years old
  - Worse prognosis than EBV-negative tumors
- Since 2008, recognized that…
  - Occurs frequently in younger patients
  - Broader morphologic spectrum than previously thought
  - Better survival than previously thought
  - (It's absurd to refer to 50-year-olds as "elderly")
- Age restriction dropped from 2016 WHO
  - Use for ***any*** EBV+ LBCL that doesn't fit a more specific category

EBV+ DLBCL ~~of the elderly~~



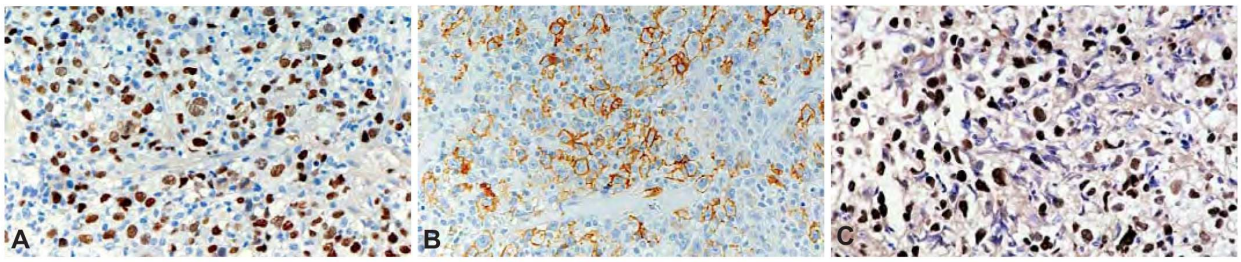
Morphologic variation:

A) Polymorphous with geographic necrosis

B) Immunoblast-like large cells admixed with small reactive lymphocytes

C) Monotonous population of HRS-like cells with prominent nucleoli

EBV+ DLBCL ~~of the elderly~~



IHC/ISH:

A) EBNA-2: positive (nuclear)

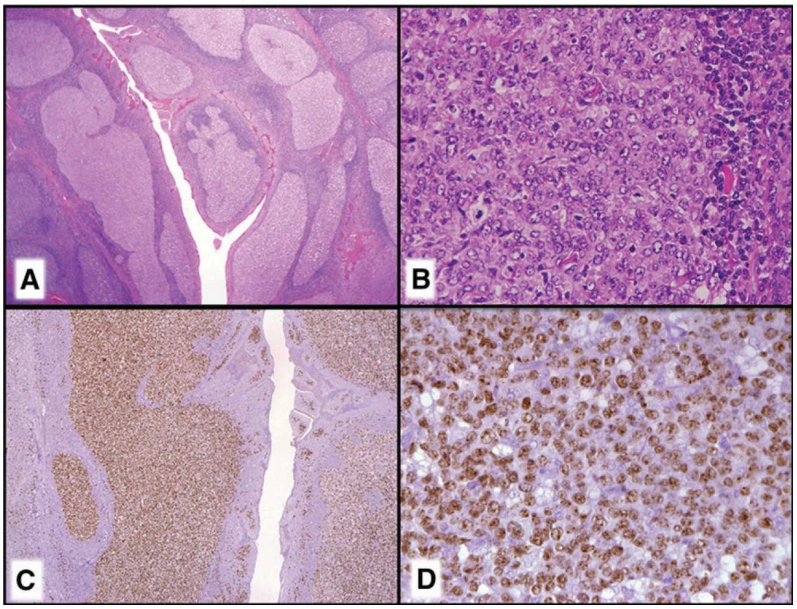
B) CD20: usually positive; subset may be negative

C) EBER ISH: positive

Large B cell lymphoma with IRF4 rearrangement

- Rare subtype of LBCL that can have diffuse, follicular, or mixed morphology, associated with ***strong IRF4/MUM-1 expression*** and ***IRF4 gene rearrangement***
- Most common in children and young adults; equal sex distribution
- Frequently involves Waldeyer's ring and/or cervical LN (less common: GI tract)
- Medium-sized to large neoplastic cells with open chromatin and small nucleoli
- Often "triple-positive" for all three Hans markers (CD10, BCL-6, IRF4/MUM-1)
  - ➢ This immunophenotype should prompt screening for IRF4 rearrangement
- Rearrangement usually to IGH; cytogenetically cryptic and often missed
- Good prognosis following immunochemotherapy +/- radiation
- DDx: **pediatric-type FL**; other types of DLBCL
  - ➢ Distinction from pediatric-type FL key (local management)

Large B cell lymphoma with IRF4 rearrangement



Low power view highlights abnormal and distended follicles (A)

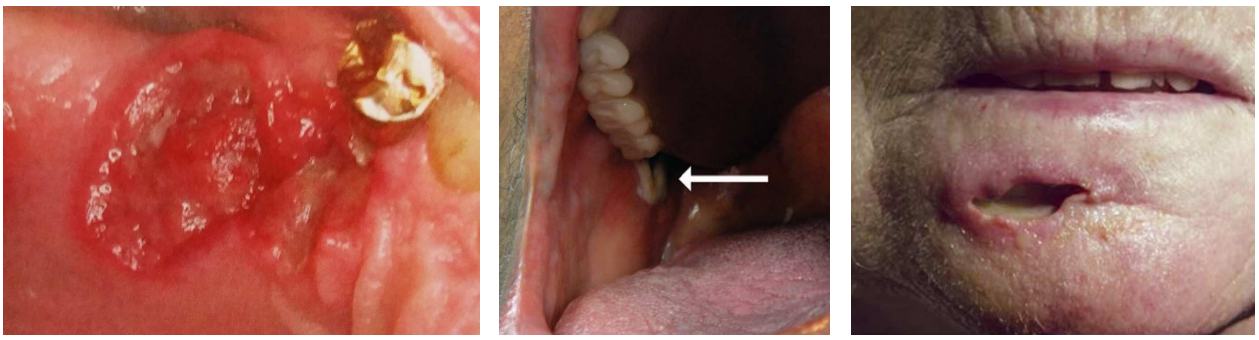
High power view shows transformed cells (B) that are positive for IRF4/MUM-1 (C) and for BCL-6 (D)

Swerdlow SH, *et al* (2016). *Blood* 127(20): 2375-90

EBV+ mucocutaneous ulcer

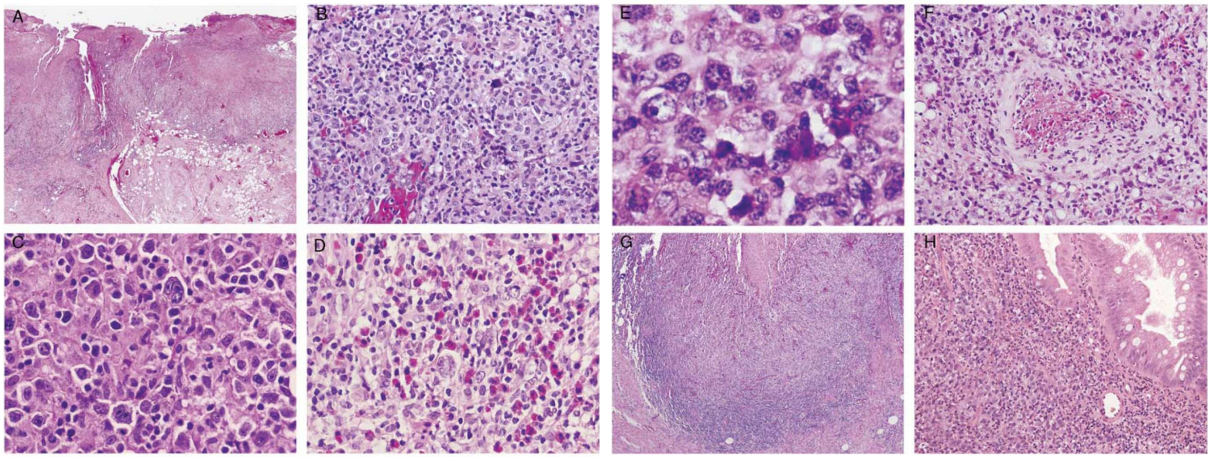
- Large B cell lymphoma occurring on cutaneous and/or mucosal sites in immunosuppressed patients (age-related or iatrogenic)
  - Reported in patients receiving methotrexate, azathioprine, cyclosporine, TNFα inhibitors, and in solid organ transplant recipients
  - Oral cavity (including gingiva) is most common site of presentation
  - Outgrowth may be related to local trauma or inflammation
- Ulcerated surface (may have pseudoepitheliomatous hyperplasia) with underlying infiltrate of large, transformed cells (resemble HRS cells/atypical immunoblasts) admixed with small lymphocytes and inflammatory cells
- Activated B cell phenotype (IRF4/MUM-1 positive, CD10 and BCL-6 negative); EBER positive in both large transformed cells and small lymphocytes
- Response to reduction in immunosuppression seen in nearly all reported cases

EBV+ mucocutaneous ulcer: Gross pathology



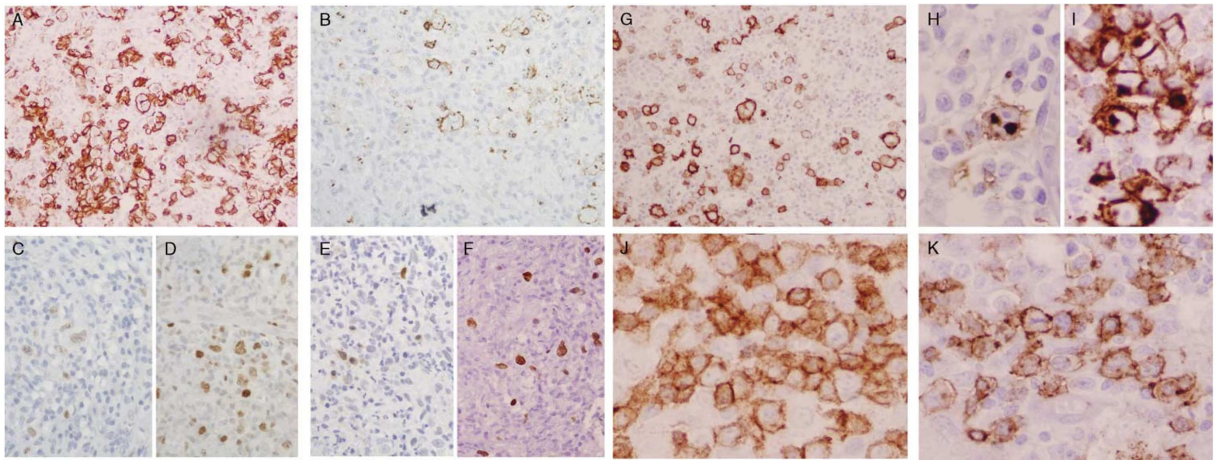
Lesions involving palate (left), gingiva (center), and skin (right)

EBV+ mucocutaneous ulcer: Histomorphology



Ulcerated lesion with polymorphous inflammatory infiltrate containing large, pleomorphic cells

EBV+ mucocutaneous ulcer: Immunophenotype



CD20 (A and B); PAX-5 (C); Oct-2 (D); BOB-1 (E); MUM-1 (F);
CD30 (G); CD15 (H, I); CD3 (J); CD8 (K)

How we sign out DLBCL

DIFFUSE LARGE B-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED (see NOTE)
Morphologic appearance : DLBCL-like
Cell-of-origin by IHC (Hans) : Germinal center B-cell-like vs non-germinal center B-cell-like
(use ≥30% as positive for CD10, BCL6 and MUM-1 per original paper)
BCL2/MYC double-expressor (IHC) : Yes if MYC ≥40% and BCL2 ≥50% in lesional cells
Cytogenetics : Describe

<MORPHOLOGIC DESCRIPTION>

<IHC DESCRIPTION>

<FLOW CYTOMETRY DESCRIPTION>

<CYTOGENETICS DESCRIPTION>

NOTE:
The morphologic, immunophenotypic and genetic features are consistent with the above diagnosis, which is categorized per the 2016 WHO revision (see ref). Correlation with clinical and other laboratory findings is advised.

Ref: Swerdlow SH et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 19 MAY 2016. 127(20): 2375-2390.