# 2016 revision of WHO classification of lymphoid neoplasms

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*TSMU*

Review Series

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

# The 2016 revision of the World Health Organization classification of lymphoid neoplasms

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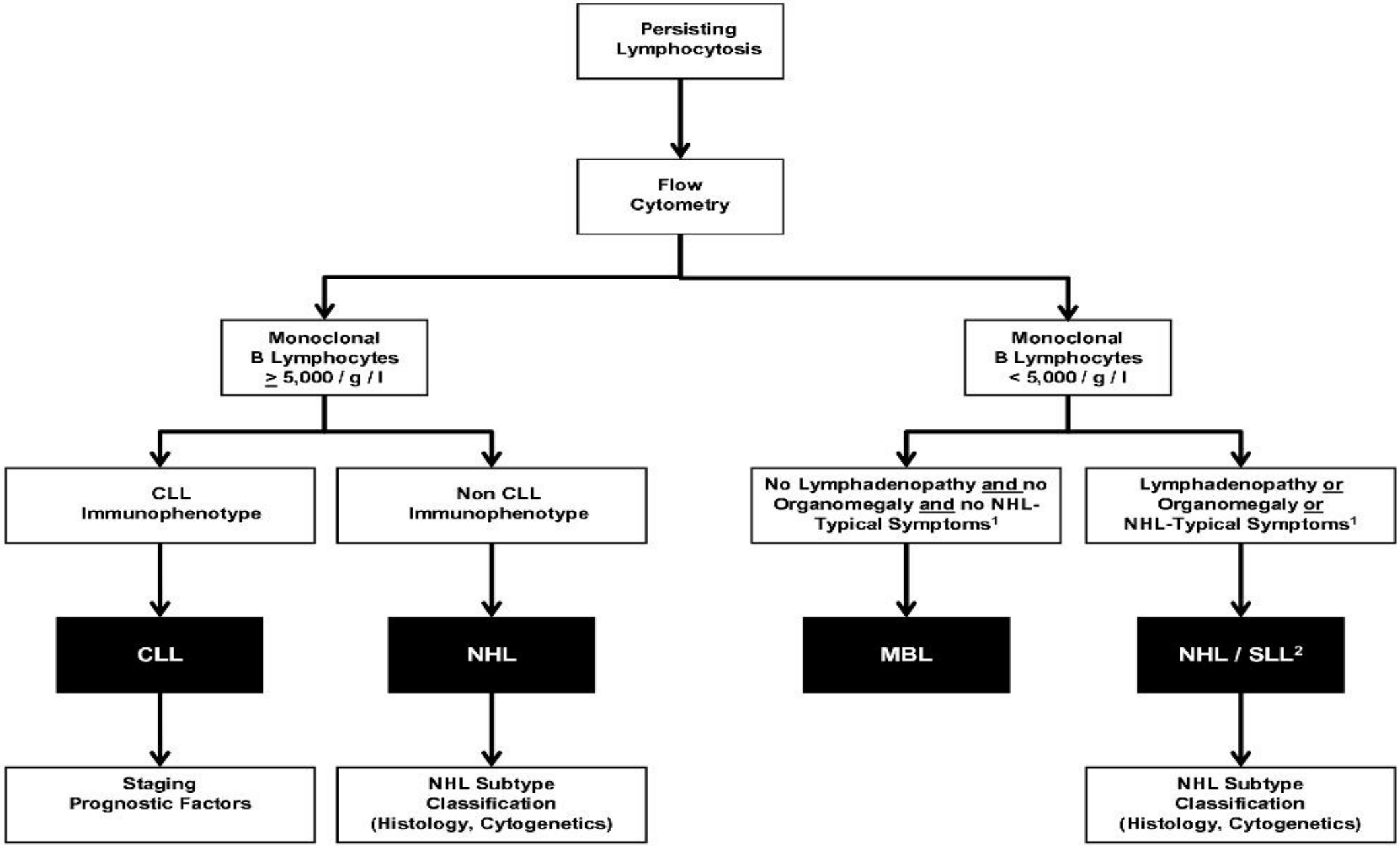
**A revision of the nearly 8-year-old World Health Organization classification of the lymphoid neoplasms and the accompanying monograph is being published. It reflects a consensus among hematopathologists, geneticists, and clinicians regarding both updates to current entities as well as the addition of a limited number of new provisional entities. The revision clarifies the diagnosis and management of lesions at the very early stages of lymphomagenesis, refines the diagnostic criteria for some entities, details the expanding genetic/molecular landscape of numerous lymphoid neoplasms and their clinical correlates, and refers to investigations leading to more targeted therapeutic strategies. The major changes are reviewed with an emphasis on the most important advances in our understanding that impact our diagnostic approach, clinical expectations, and therapeutic strategies for the lymphoid neoplasms. (*Blood*. 2016;127(20):2375-2390)**

## Introduction

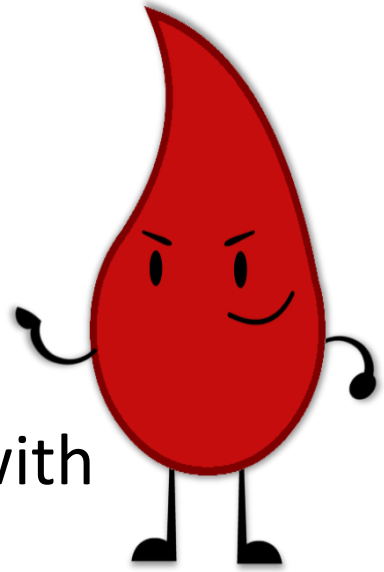
# MATURE B-CELL LYMPHOID NEOPLASMS

## Monoclonal B-cell lymphocytosis

- 2008 year_monoclonal B cell population <5,000 per $mm^3$ with pheno type CLL, atypical-CLL, non-CLL(CD5-)B cells;
- Nowadays_CLL phenotype (70%) (CD5,CD19,CD23+)B-cell lymphocy tes < 5.000 per $mm^3$ (but not 0) no lymphoproliferative disorders;
- Count_ "high-count"MBL precedes virtually all cases of CLL/small lym phocytic lymphoma (SLL). requires routine/yearly follow-up.
- $CD5^-$ MBL _ many similarities with marginal zone lymphoma especial ly splenic.


Persisting Lymphocytosis
Flow Cytometry
Monoclonal B Lymphocytes ≥ 5,000 / g / l
Monoclonal B Lymphocytes < 5,000 / g / l
CLL Immunophenotype
Non CLL Immunophenotype
No Lymphadenopathy and no Organomegaly and no NHL-Typical Symptoms[1]
Lymphadenopathy or Organomegaly or NHL-Typical Symptoms[1]
CLL
NHL
MBL
NHL / SLL[2]
Staging Prognostic Factors
NHL Subtype Classification (Histology, Cytogenetics)
NHL Subtype Classification (Histology, Cytogenetics)

# In-situ follicular neoplasia



- 2008 year_In situ follicular lymphoma;
- ISFN_low rate of progression, but are more often associated with prior or synchronous overt lymphomas;
- Difficultly differentiated_ isolated ISFN or follicular center involve ment by FL;
- Problems_t(14;18)(q32;q21) IGH/BCL2 translocation may reside in germinal centers;
- Higher levels of circulating $t(14;18)^{+}$ lymphocytes ($>10^{-4}$ of total cells) indicate a higher risk for FL.

# Pediatric type Follicular Lymphoma

- ~~Pediatric lymphoma~~
- Adults are also affected;
- Follicles that often have prominent blastoid follicular center cells rather than classic centroblasts (or centrocytes);
- BCL2 protein expression;
- MAP2K1 gene mutation;
- Avoid underdiagnosing conventional grade 3 FL;
- Might be a “benign clonal proliferation with low malignant potential;
- No additional treatment only excision.

# Duodenal type follicular lymphoma

- Distinct from other GI Follicular Lymphoma;
- Features overlap ISFN and MALT marginal zone lymphoma;
- Excellent outcome and prognosis.

# LargeB-cell lymphoma(LBCL)with IRF4 rearrangement

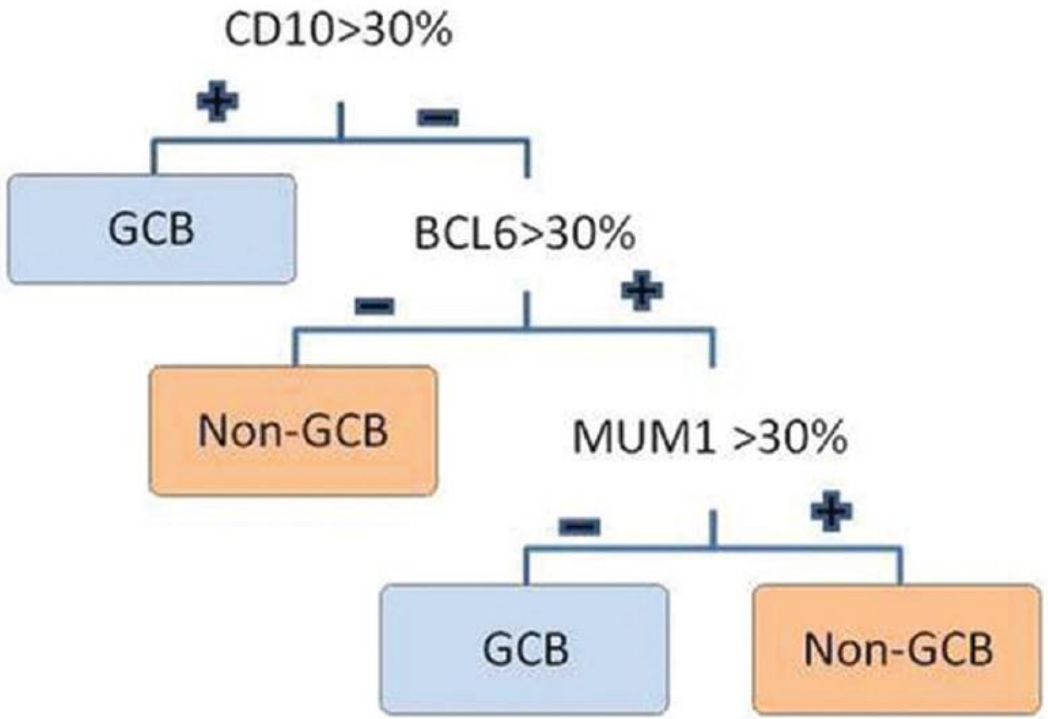
- In children and young adults ,
- Waldeyer ring and/or cervical lymph nodes are most common sites and are low stage
- Follicular, follicular and diffuse, or pure diffuse growth pattern resembling FL grade 3B or a DLBCL.
- Strong IRF4/MUM1 expression and translocation is seen usually with BCL6;
- BCL2 and CD10 are also expressed in more than half of the cases with a minority CD51.
- DD with $CD10^{-}$ $IRF/MUM1^{+}$ lymphomas in olders.

# Mantle cell lymphoma

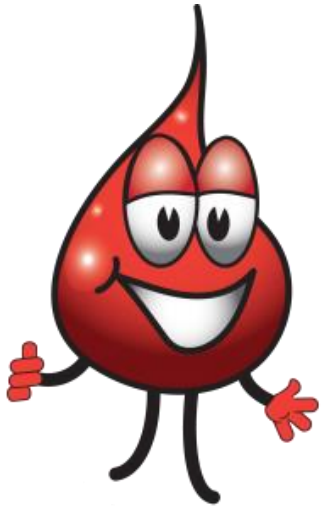
- Developed in a linear fashion from naive B cells
- IGHV-un mutated or minimally mutated B cells that usually express SOX11 and typically involves lymph nodes and other extranodal sites.
- Other MCL develop from IGHV-mutated $SOX11^-$ B cells which leads to leukemic non-nodal MCL, usually involving the PB, bone marrow, and often spleen.
- Cyclin D11 cells, most typically in the inner mantle zones of follicles, in lymphoid tissues that do not otherwise suggest the diagnosis of a MCL, and is often found incidentally.

# Diffuse large B cell lymphoma

- Germinal center B-cell-like (GCB) and activated B-cell-like (ABC) based on GEP (gene expression profile);




*Hans algorithm*



- The better understanding of the molecular pathogenesis of these 2 subgroups since 2008 has led to the investigation of more specific therapeutic strategies;
- Prospective trials are ongoing to determine whether these therapies should be incorporated into clinical practice;
- MYC protein expression (30%-50%) and is associated with concomit ant expression of BCL2 in 20% to 35% of cases;
- Most off them “double-expressor lymphoma”;
- Most studies use a cutoff of 40% MYC-expressing cells to define these cases.

- Worse outcome than other DLBCL;
- Common somatic mutations:

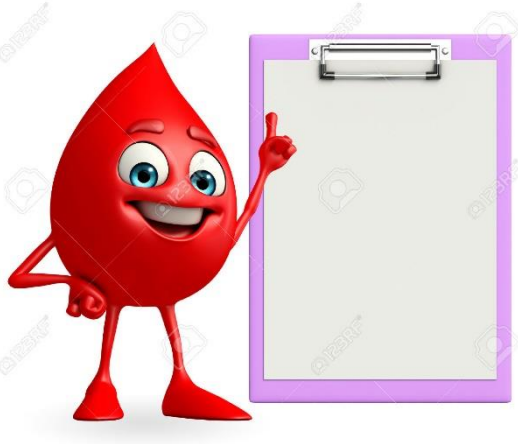
1. GCB-DLBCL carry frequent alteration in the histone methyl transferase EZH2, BCL2 translocations, and mutations in the cell motility regulator GNA13
2. ABC-DLBCL have mutations in genes (MYD88, CD79A, CARD11, TNFAIP3) activating the B-cell receptor/Toll-like receptor and NF-kB pathways

# EBV1 large B-cell lymphomas NOS and EBV1 mucocu taneous ulcer

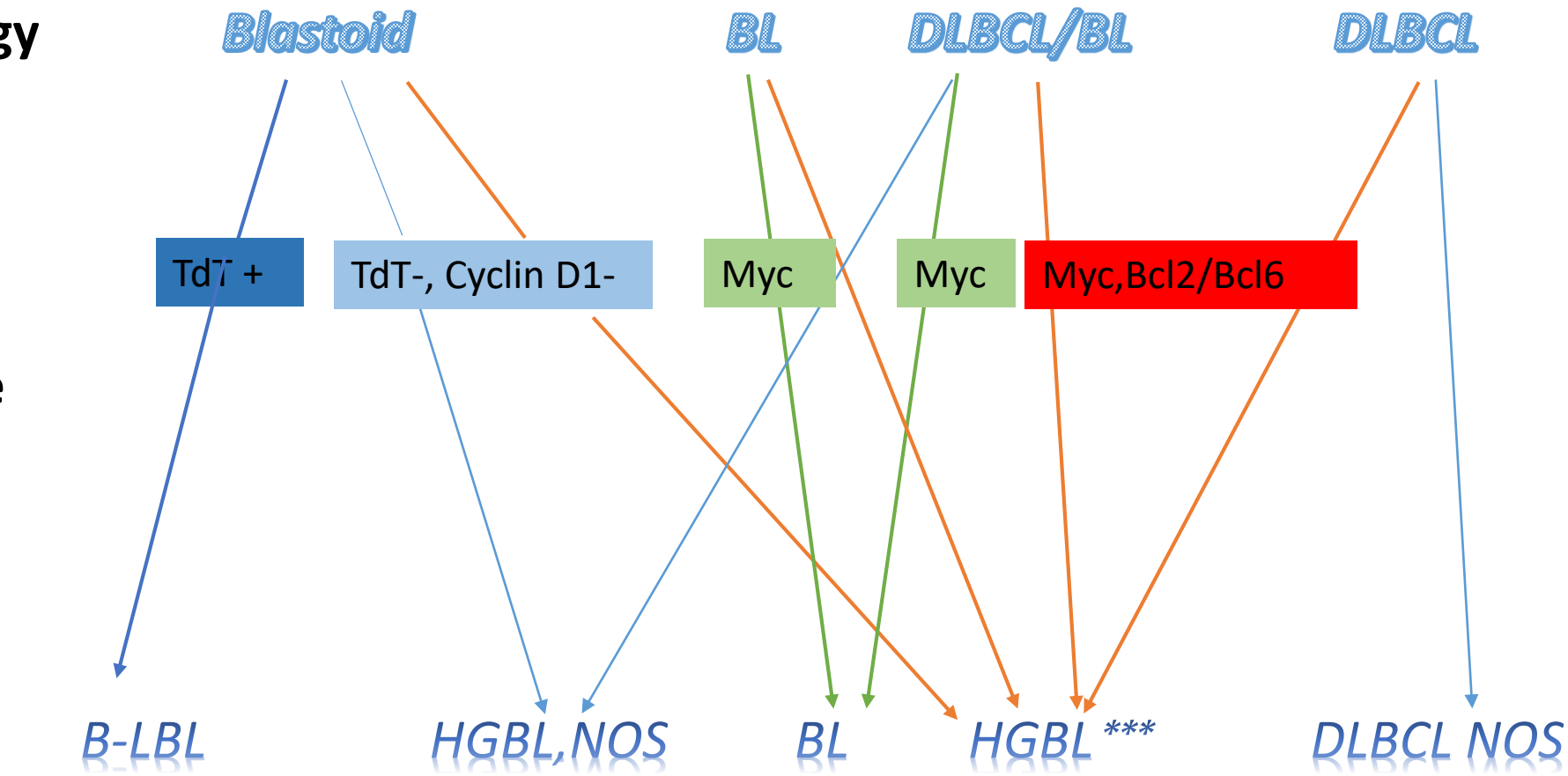
- Have been increasingly recognized in younger patients, with a broa der morphological spectrum and better survival than initially thought;
- Lymphomatoid granulomatosis;
- EBV+ mucocutaneous ulcer - Self limited growth potential and respo nse to conservative management.

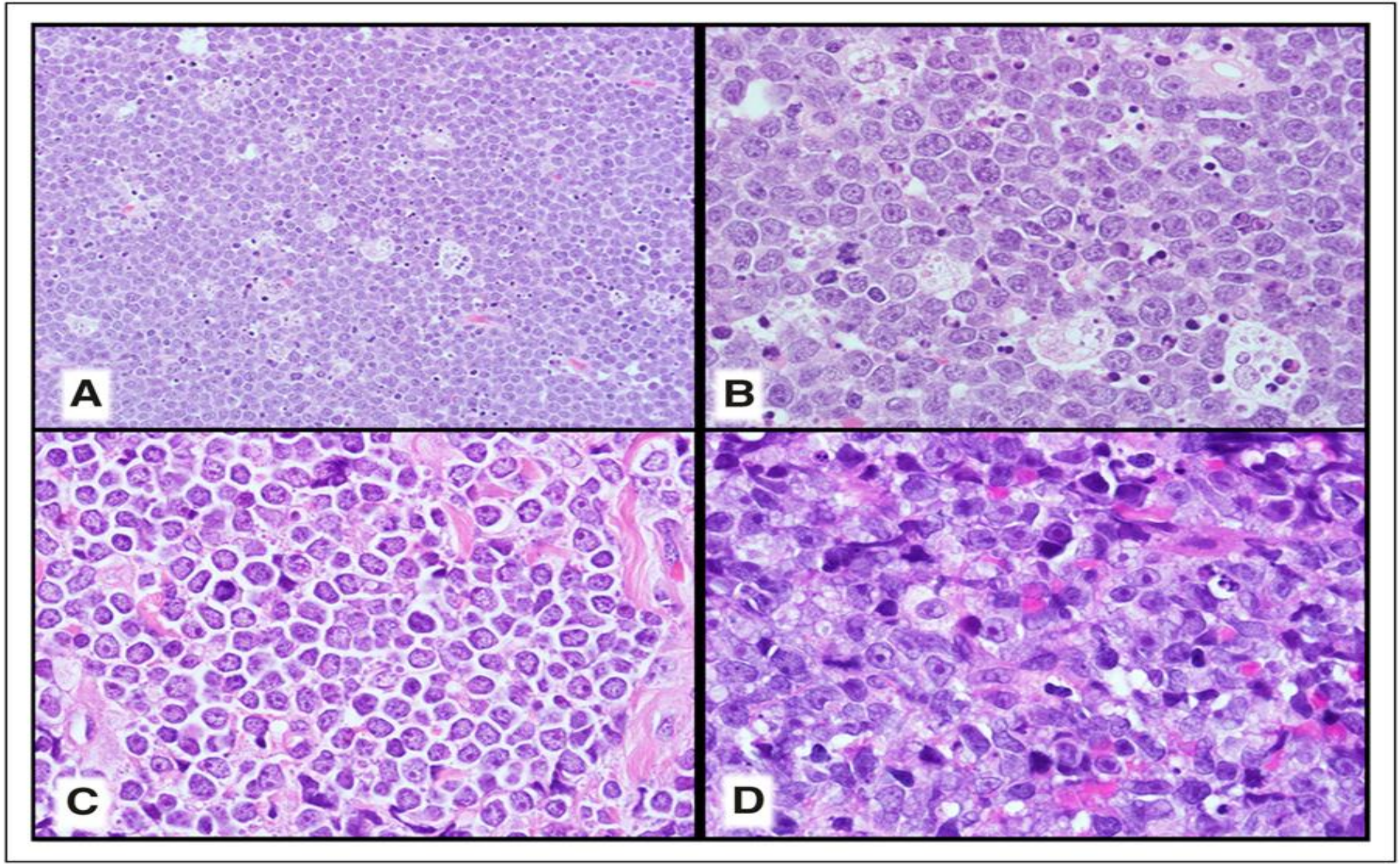
# Burkitt lymphoma with 11q aberration

- Lymphomas that resemble BL morphologically, to a large extent phe notypically and by GEP, but which lack MYC rearrangements;
- 11q alteration characterized by proximal gains and telomeric losses;
- Lower levels of MYC expression, a certain degree of cytological pleo morphism, occasionally a follicular pattern, and frequently a nodal presentation.



# High-grade B-cell lymphomas, with and without MYC and BCL2 or BCL6 translocations***




A
B
C
D


Thank
You!