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Turkish Society of Hematology
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EHA-TSH Hematology Tutorial on Lymphoma

Self-assessment Case – Session [1]

Speaker: Ayşegül Üner

İzmir, Turkey
April 6-7, 2019

Introduction

- 56 year old male patient
- July 2014- Painful cervical lymphadenopathy (LAP) without history of fever, night sweats or weight loss.
- Corticosteroids were administered twice (between August-October 2014 and December 2014 –March 2015) which resulted in regression of LAP. However in both instances there was enlargement of the lymph nodes once the steroids were ceased
- Laboratory tests
  - LDH: 196 IU/L (<240)
  - Beta-2: 1.98 mg/dl (<2.5)
  - CBC: Normal

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Medical History

- **Allergy:** Penicilin, acetylsalicylic acid, moxifloxacin, paracetamol
- **Medications:** metformin 2x1000mg, losartan potassium 50mg, Metoprolol Suksinat 50mg, Amylodipin + Valsartan

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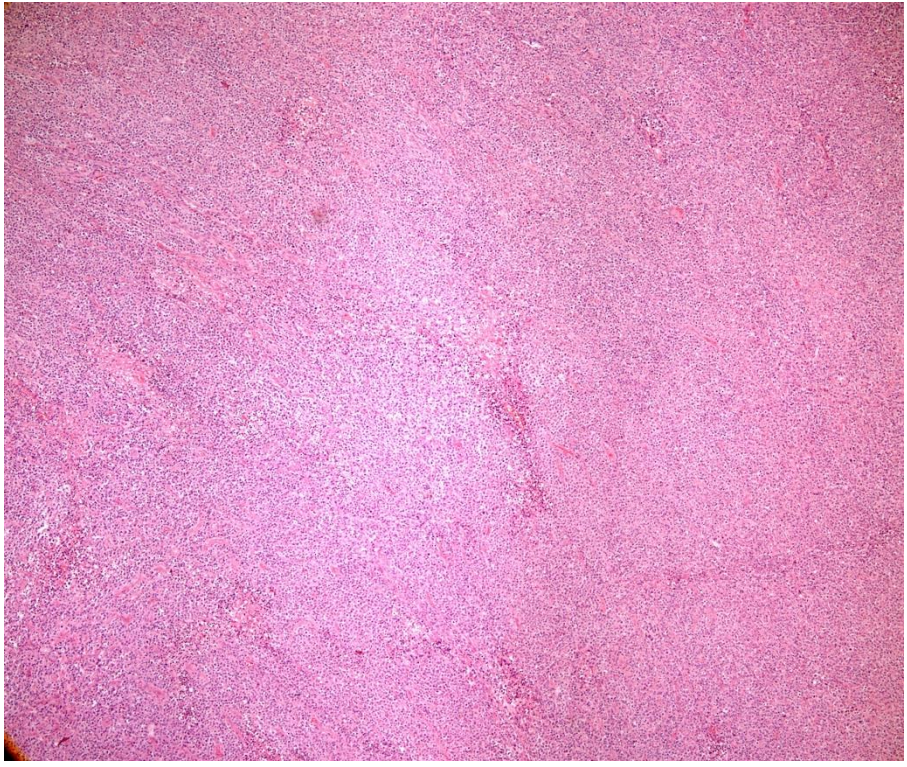
Lymph node biopsy



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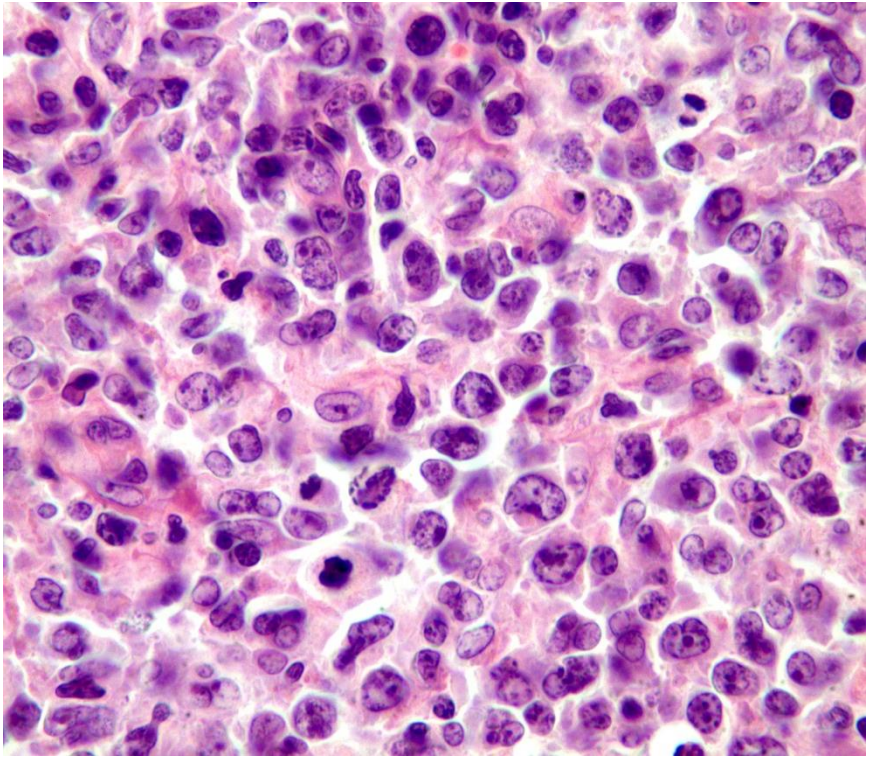
Lymph node biopsy



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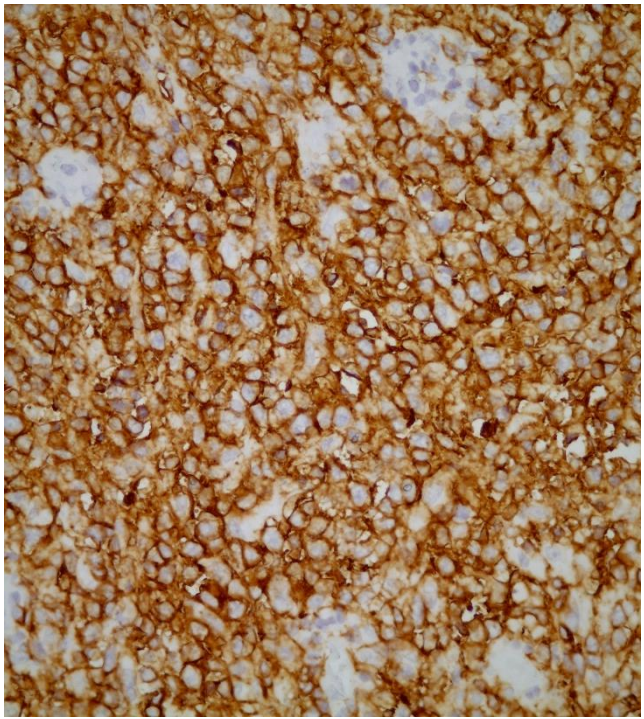
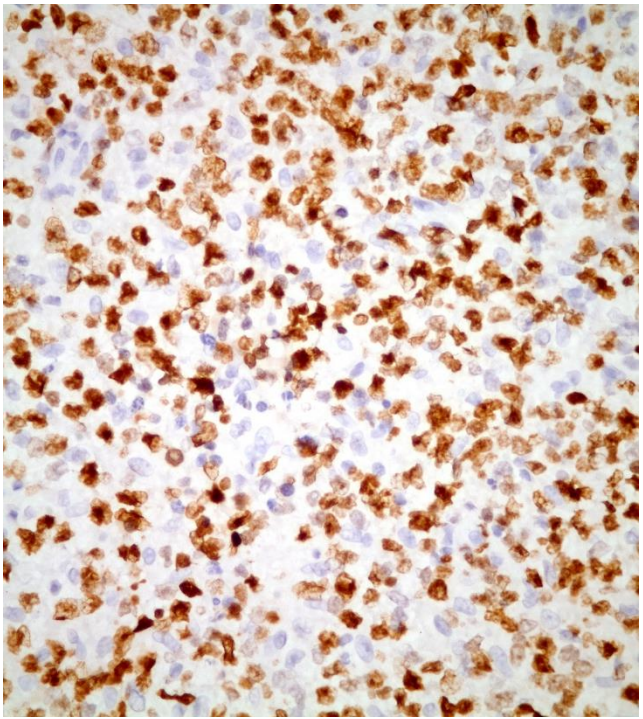


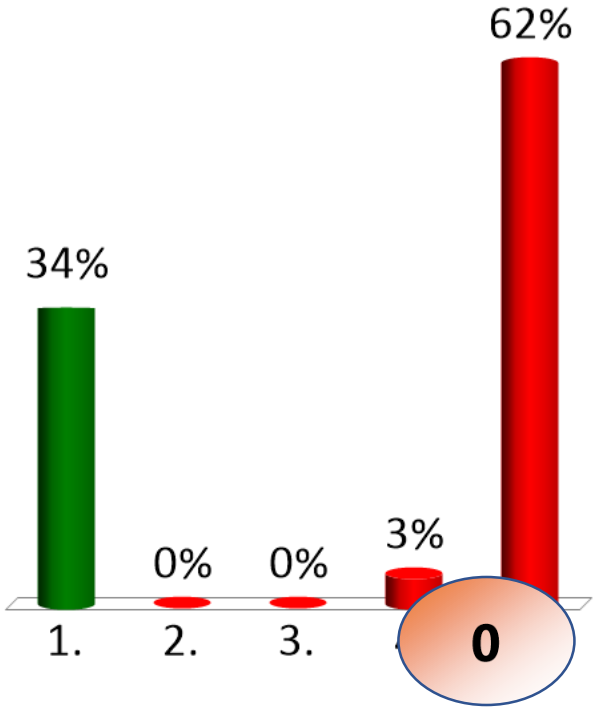
CD20

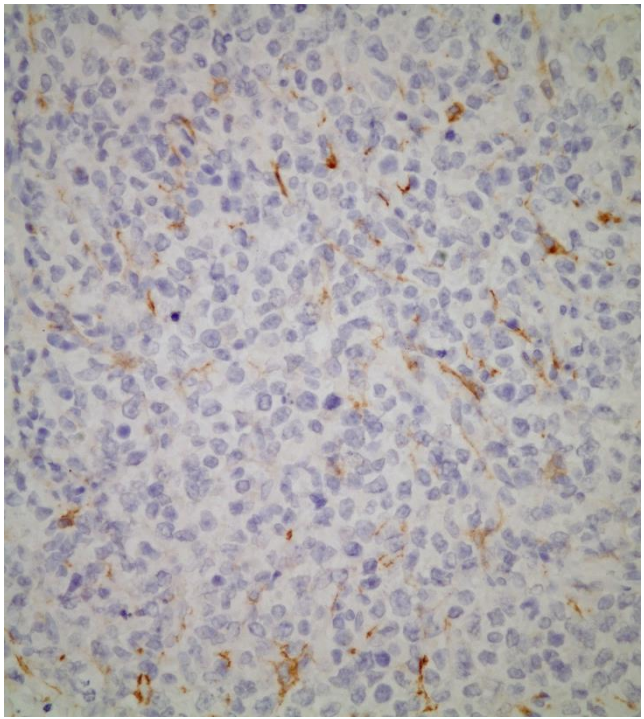


Ki-67

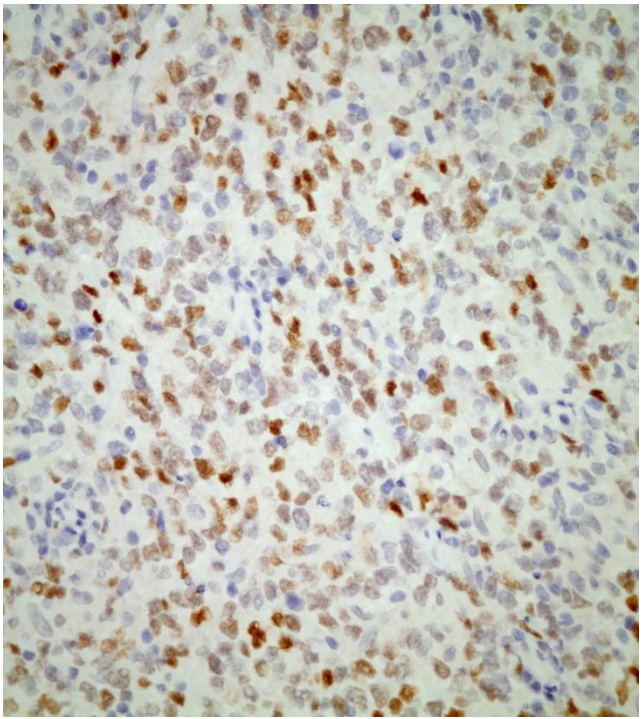
Q1) Based on the morphologic and immunophenotypic features the case is diagnosed **as Diffuse Large B Cell Lymphoma.**
What other information should be provided in the pathology report according to the WHO 2016 revision ?

1. Cell of origin
2. Stage
3. CD30 expression
4. CD20 expression
5. Level of Myc expression

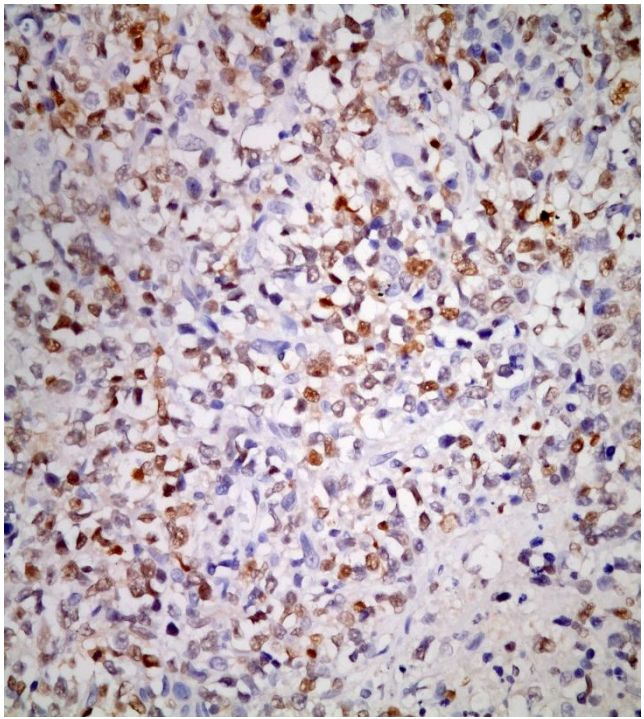




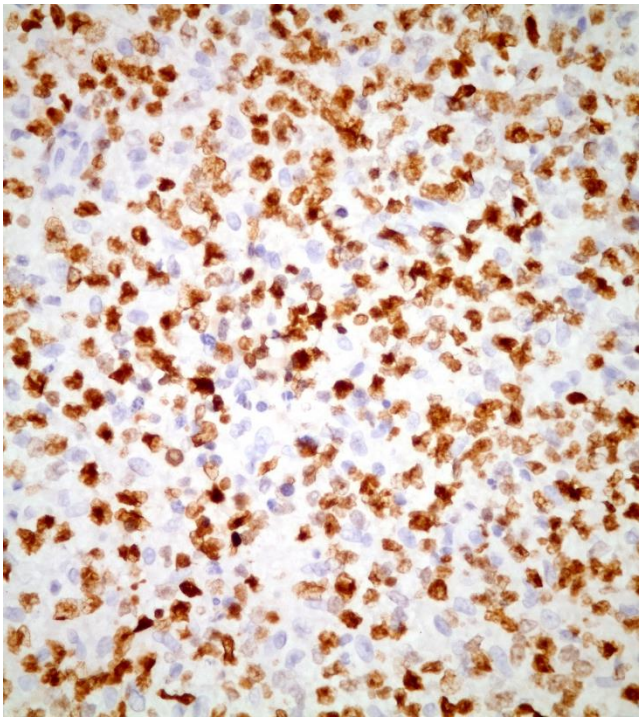
CD10



Bcl-6



MUM-1



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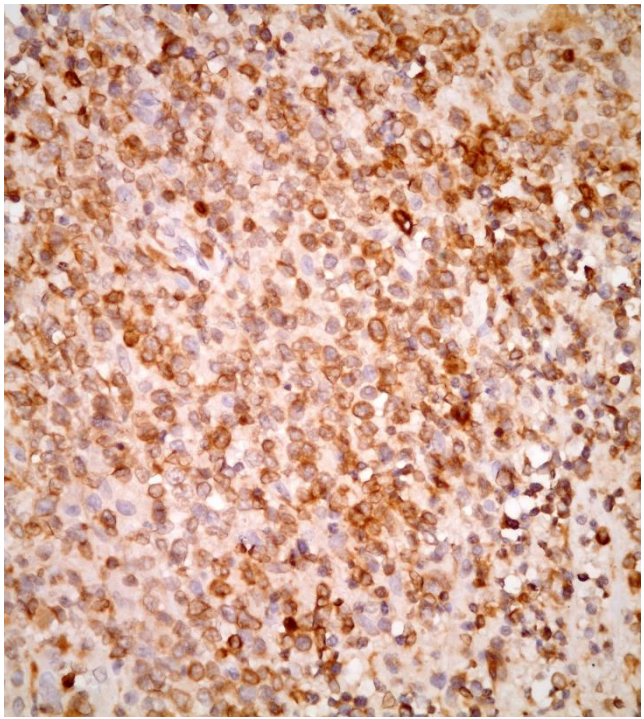
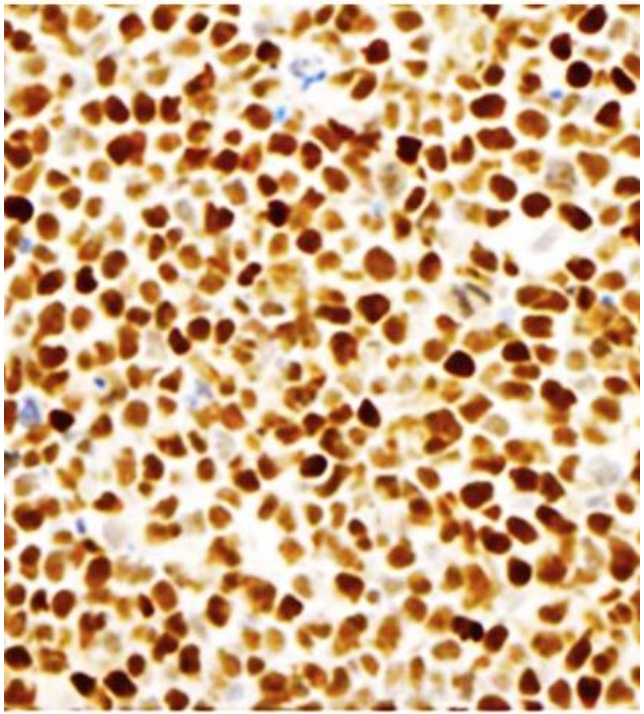


Bcl-2



MYC

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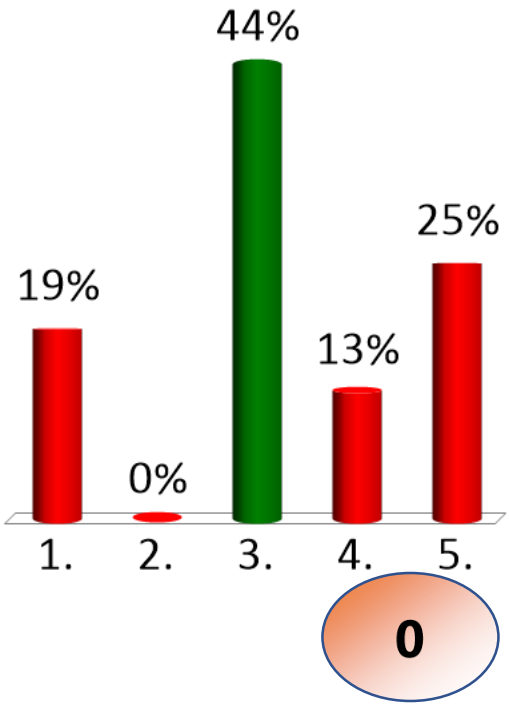
Summary of immunohistochemical analysis

- The neoplastic cells are positive for **CD20, bcl-6, MUM-1**, and negative for **CD30 and CD10.**
- More than 70% of the cells expressed **Bcl-2** and **Myc**.
- MIB-1 index was around 90%

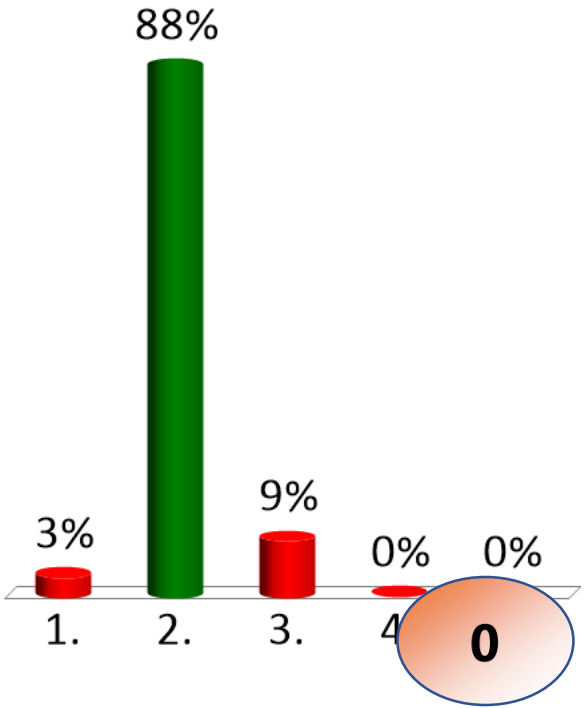
Q2) According to these results, this case should be diagnosed as:

1. DLBCL, Germinal-centre phenotype
2. Primary mediastinal Large B-cell lymphoma
3. DLBCL, non-Germinal centre phenotype
4. DLBCL, Double-hit
5. High grade B-cell lymphoma with features intermediate between DLBCL and BL, not further classified



Q3) Which other test(s) would you request before deciding how to treat this patient?

1. B-cell clonality assay
2. Break-apart FİSH test for MYC, BCL-2 and BCL-6
3. EBER *in situ* hybridization test for EBV
4. In situ hybridization for kappa and lambda light chains
5. Serum ferritin assay



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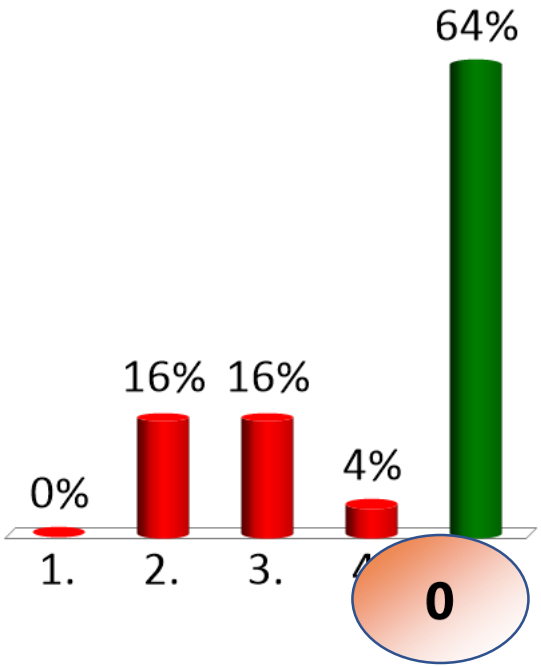
Further investigations

- The case is a double-expressor (Myc and Bcl-2) according to the immunohistochemical analysis
- FISH: *MYC, BCL-6* and *BCL-2* break-apart probes
  - No evidence of break
- No evidence of bone marrow involvement, Bone marrow biopsy

Q4) What is the significance of Double Expressor (DE) status in a case which is not double-hit or triple-hit?

1. It has no prognostic value
2. DE cases behave as bad as high grade B cell lymphomas with *MYC* and *BCL-2 (Double-Hit)* gene rearrangements
3. DE cases are classified under a different category in the WHO 2016 revision
4. There is no biologic overlap between DE and Double-Hit lymphomas
5. DE DLBCL's prognosis is not as bad as Double-Hit or Triple-Hit Lymphomas



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Follow up

- Stage I
- 4 courses of R-CHOP and Lenalidomide
- Patient is in remission for the last four years

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Feedback

Q1 COO information should be included in the pathology report for all cases of DLBCL according to the 2016 revision of WHO Classification

Q2 The most practical method to determine COO is immunohistochemical analysis to identify expression of various relevant proteins. Hans Classifier which includes three markers (CD10, MUM-1 and Bcl-6) is one of the most commonly used algorithms worldwide.

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Feedback

Q3 In cases with high level of Myc expression by immunohistochemistry, FISH analysis for *MYC, BCL-2* and *BCL-6* should be performed to determine whether they are double-hit or triple-hit lymphomas

Q4 DE DLBCL's are not considered a separate category in the WHO 2016 revision. It is considered to have a prognostic significance. DE cases have intermediate prognosis between DLBCL's that do not have a DE status and those which are double-hit.

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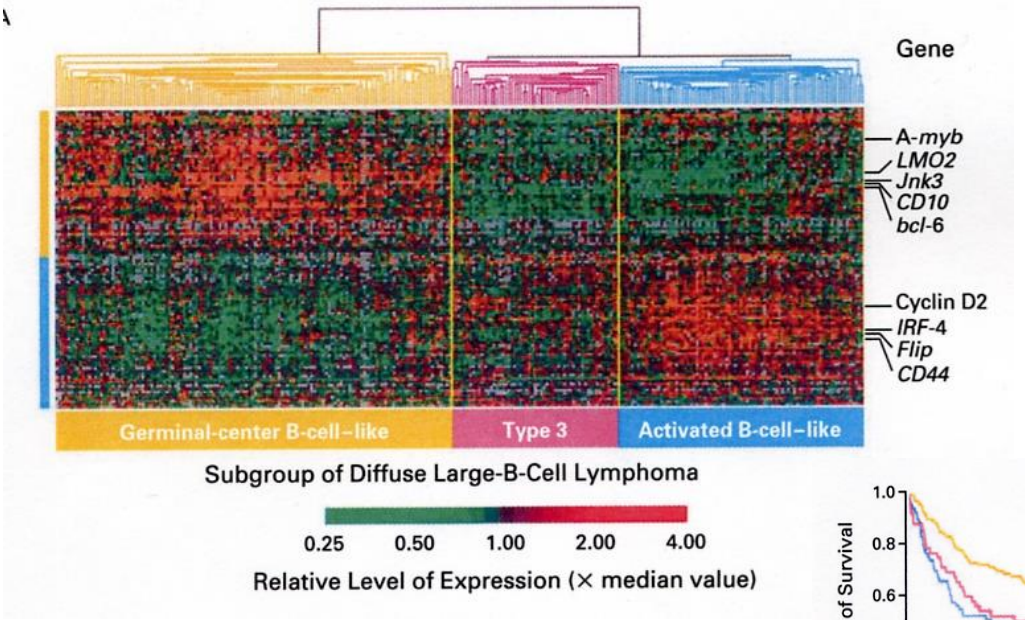
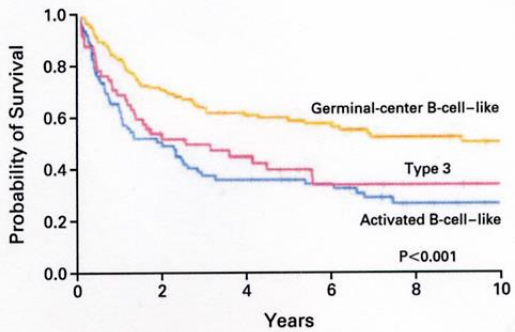
Discussion





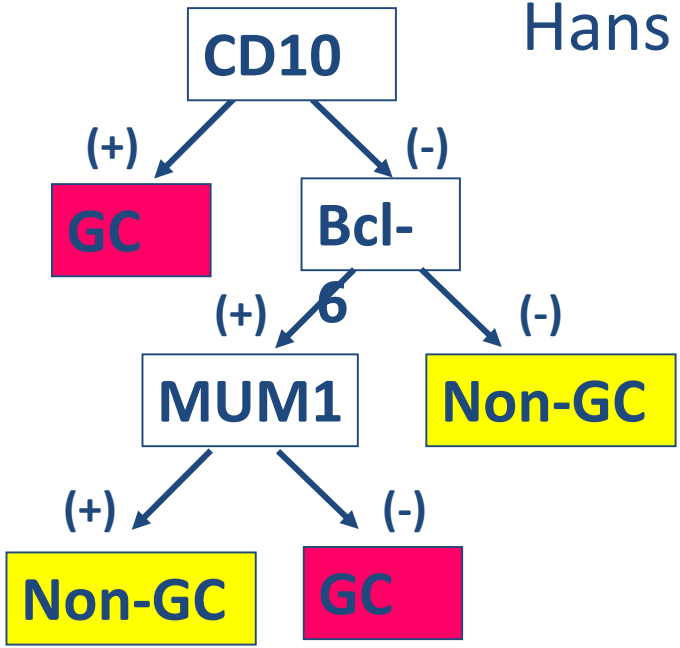
Rosenwald A, et al: NEJM 346:1937, 2002

WHO 2016 approach to COO for DLBCL

- 2016 update recommends identification of COO for all DLBCL cases

  two subgroups are distinct in their mutational landscape, signaling pathways, and clinical outcomes
- GEP is the gold standard, however it is not practical to perform for each case
- Immunohistochemistry is the method of choice.
- No recommendation for which algorithm to use

Hans Classifier



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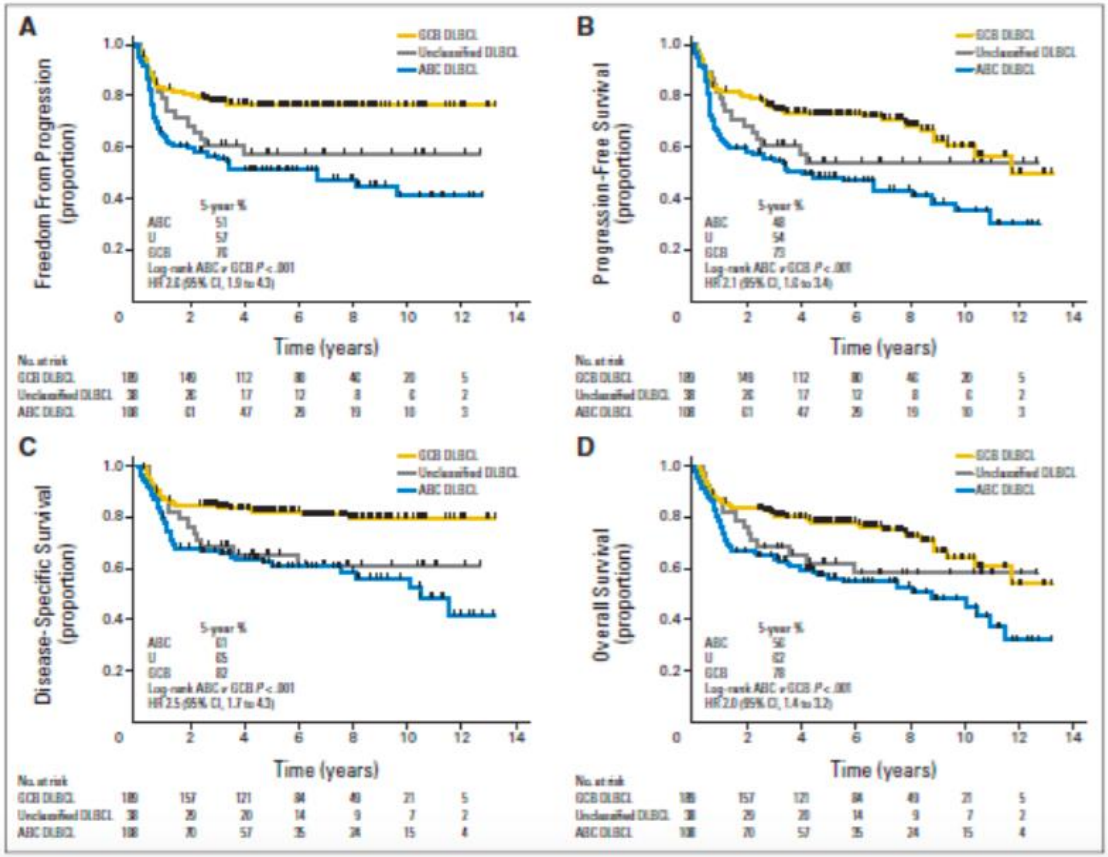
Importance of COO



Scott et al. JCO 2015

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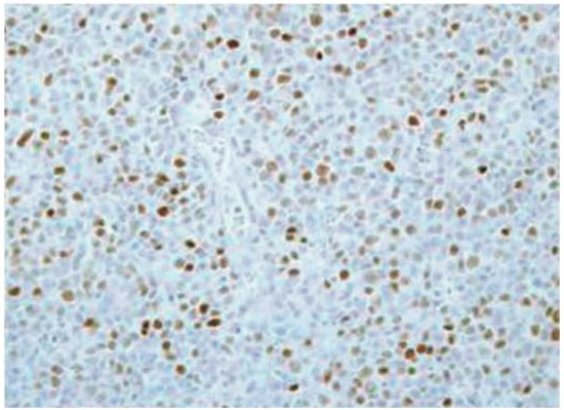
Discussion

- *Myc* expression can be demonstrated in 29-47% of the cases (different cut-offs)
- *Myc* expresion in more than 70% of the cells correlates with *MYC* rearrangement

- *MYC* rearrangement does not always correlate with protein expresion with IHC



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	Diffuse large B-cell lymphoma	B-cell lymphoma unclassifiable	Burkitt's lymphoma
BCL2 rearrangement	30–40%	78%	0%
BCL6 rearrangement	30%	ND	0%
MYC translocation	5–17%	35–90%	90–100%
BCL2–MYC rearrangement	58–85%	47–60%	0%
BCL6–MYC rearrangement	5–8%	ND	0%
BCL3–MYC rearrangement	7–16%	ND	0%
BCL2–BCL6–MYC rearrangement	16%	ND	ND
Translocation partners	Most frequently non-IG (35–53%)	Most frequently non-IG (38%)	IG (100%)
MYC copy-number gains (3–4 copies)	21–38%	ND	ND
MYC amplification (>4 copies)	2%	ND	Rare
MYC aberrant somatic mutations	32%	20%	Frequent

IG=immunoglobulin. ND=no data.

Table 1: **Frequency of common genetic abnormalities in aggressive lymphomas**

Sarkozy et al Lancet 2015

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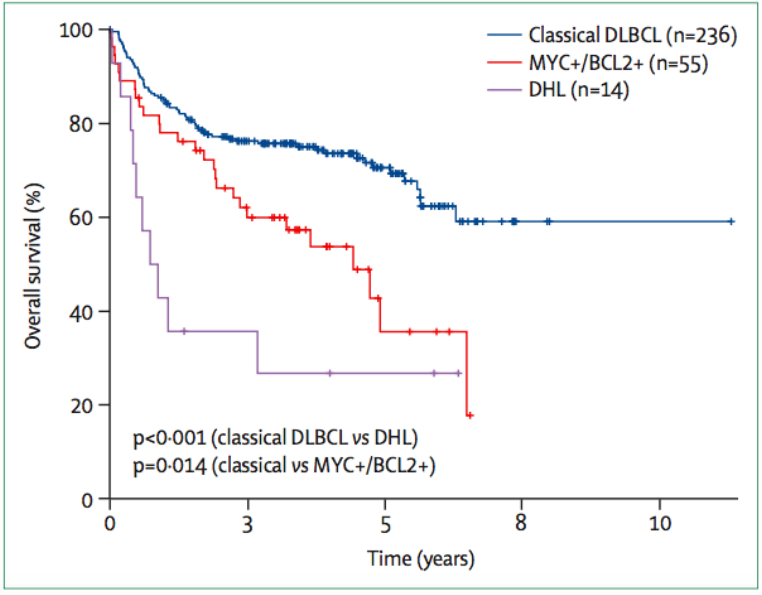
Discussion

19-34% of cases

>40% with *Myc* expression and >50% *Bcl-2* expression

Most of the cases do not have a *MYC* and *BCL2* gene alteration

Has prognostic value but does not define a separate entity



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References

1. Swerdlow SH, Campo E, Pileri S, Harris NL, Stein H, Sieber R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES (2016), The 2016 revision of the World Health Organization classification of lymphoid neoplasms, Blood 127:2375-2390. ..
2. Hans CP, Weisenburger DD, Greiner TC et al, (2004) Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray, Blood 103: 275-282,

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References

3. Scott DW, Mottok A, Ennishi D et al (2015) Prognostic Significance of Diffuse Large B-Cell Lymphoma Cell of Origin Determined by Digital Gene Expression in Formalin-Fixed Paraffin-Embedded Tissue Biopsies. *Jornal of Clinical Oncology*, **33**, 2848-2856.
4. Sarkozy C, Traverse-Glehen A, Coiffier B, Double-hit and double-protein expression lymphomas: aggressive and refractory lymphomas (2015) The Lancet Oncology 16: e555-566.