



Büyük B Hücreli Lenfomada Yinelenen Sınıflama: olgularla değerlendirme

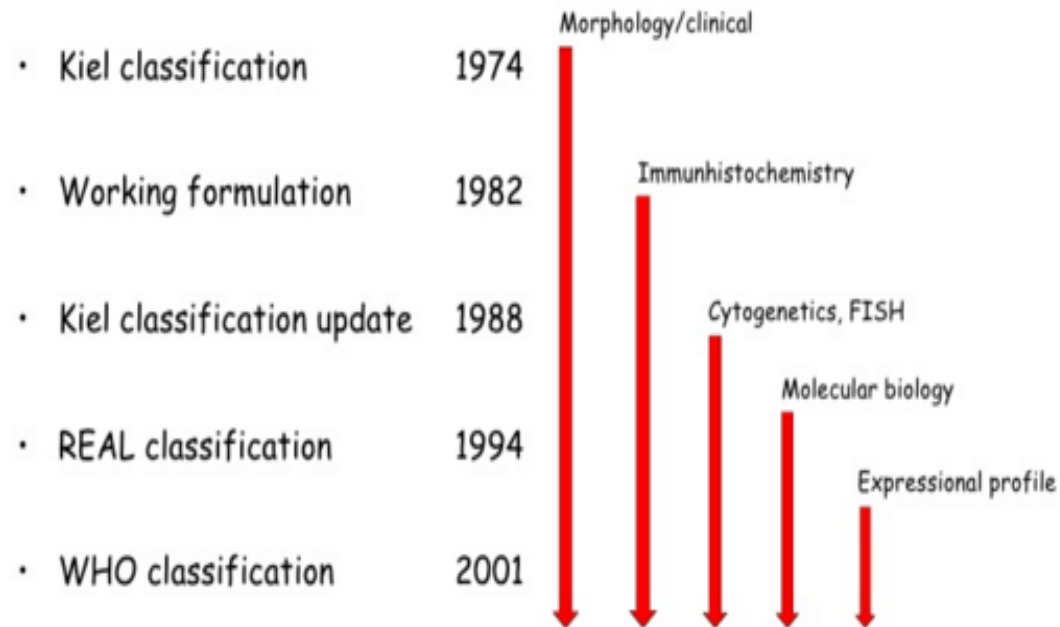
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Patoloji Anabilim Dalı



Fig. 1.1. Karl Lennert in Kiel, in 1974, standing in front of a blackboard with the first version of the Kiel classification

Historical background of lymphoma classification



Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling.

Alizadeh AA¹, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, Boldrick JC, Sabet H, Tran T, Yu X, Powell JI, Yang L, Marti GE, Moore T, Hudson J Jr, Lu L, Lewis DB, Tibshirani R, Sherlock G, Chan WC, Greiner TC, Weisenburger DD, Armitage JO, Warnke R, Levy R, Wilson W, Grever MR, Byrd JC, Botstein D, Brown PO, Staudt LM.

⊕ Author information

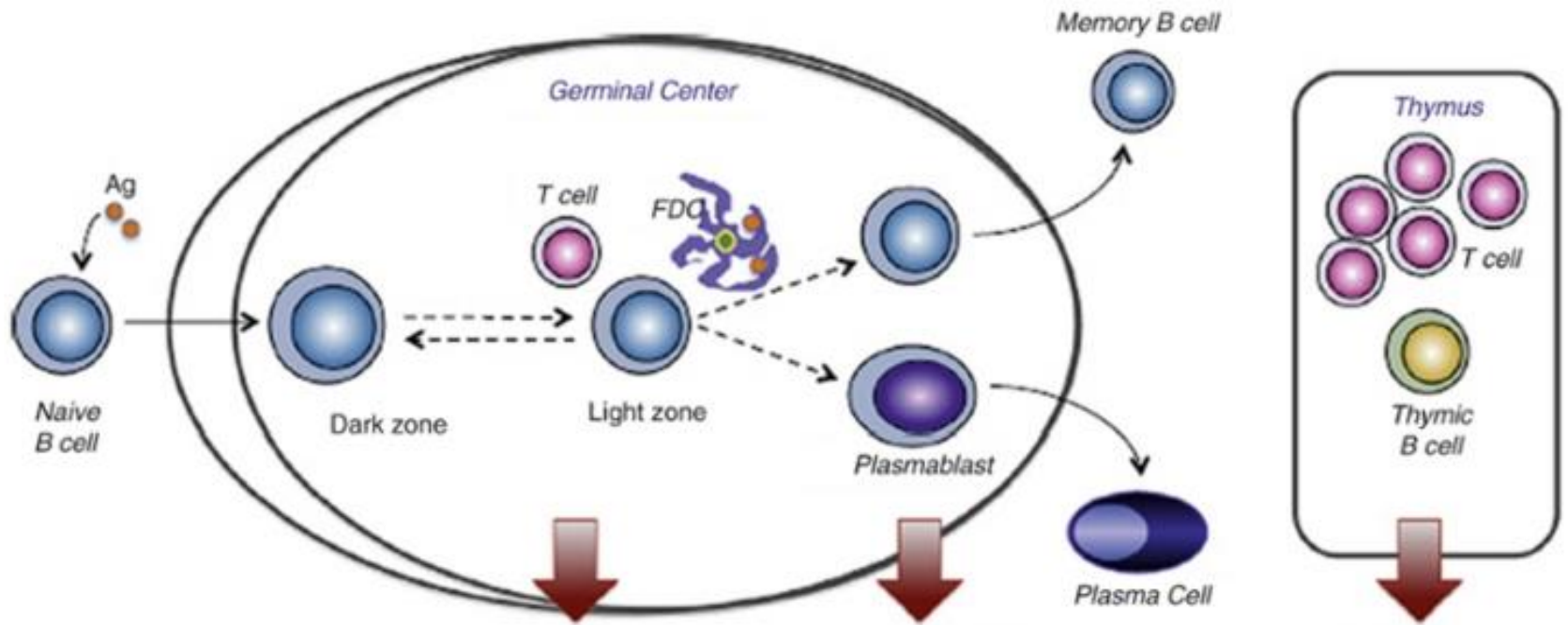
Abstract

Diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin's lymphoma, is clinically heterogeneous: 40% of patients respond well to current therapy and have prolonged survival, whereas the remainder succumb to the disease. We proposed that this variability in natural history reflects unrecognized molecular heterogeneity in the tumours. Using DNA microarrays, we have conducted a systematic characterization of gene expression in B-cell malignancies. Here we show that there is diversity in gene expression among the tumours of DLBCL patients, apparently reflecting the variation in tumour proliferation rate, host response and differentiation state of the tumour. We identified two molecularly distinct forms of DLBCL which had gene expression patterns indicative of different stages of B-cell differentiation. One type expressed genes characteristic of germinal centre B cells ('germinal centre B-like DLBCL'); the second type expressed genes normally induced during *in vitro* activation of peripheral blood B cells ('activated B-like DLBCL'). Patients with germinal centre B-like DLBCL had a significantly better overall survival than those with activated B-like DLBCL. The molecular classification of tumours on the basis of gene expression can thus identify previously undetected and clinically significant subtypes of cancer.

Comment in

Gene expression in diagnosis. [Nature. 2000]

How diagnosis with microarrays can help cancer patients. [Nature. 2000]



GCB- and ABC-DLBCL			GCB-DLBCL			ABC-DLBCL			PMLBCL		
		%			%			%			%
	BCL6 Tx	20-40		BCL2 Tx/M	34		TNFAIP3 M/D	30		PDL1/2 Amp/Tx	49
	MLL2/MLL3 M	32-38		GNA13 M	25		MYD88 M	30		SOCS1 M	45
	CREBBP/EP300 M/D	32		EZH2 M	22		CDKN2A/B D	30		CIITA Tx	38
	B2M/CD58 M/D	21-29		BCL6 BSE1 M	15		BCL2 Amp	24-30		STAT6 M	36
	TP53 M	20		MYC Tx	10		PRDM1 M/D	25		TNFAIP3 M	36
	MEF2B M	10		miR17-92 G	6-12		CD79A/B M	20		JAK2 Amp	30
	FOXO1 M	8		PTEN D	6-11		CARD11 M	9		TP53 M	20
										PTPN1 M	20

■ Epigenetic modification	■ Proliferation	■ BCL6 deregulation	■ NF-κB/BCR signaling	■ DNA damage response
■ Immune escape	■ Apoptosis	■ Terminal differentiation	■ JAK/STAT signaling	■ Cell cycle
				■ Other

%50 GCB, %30-40 ABC, %15-20

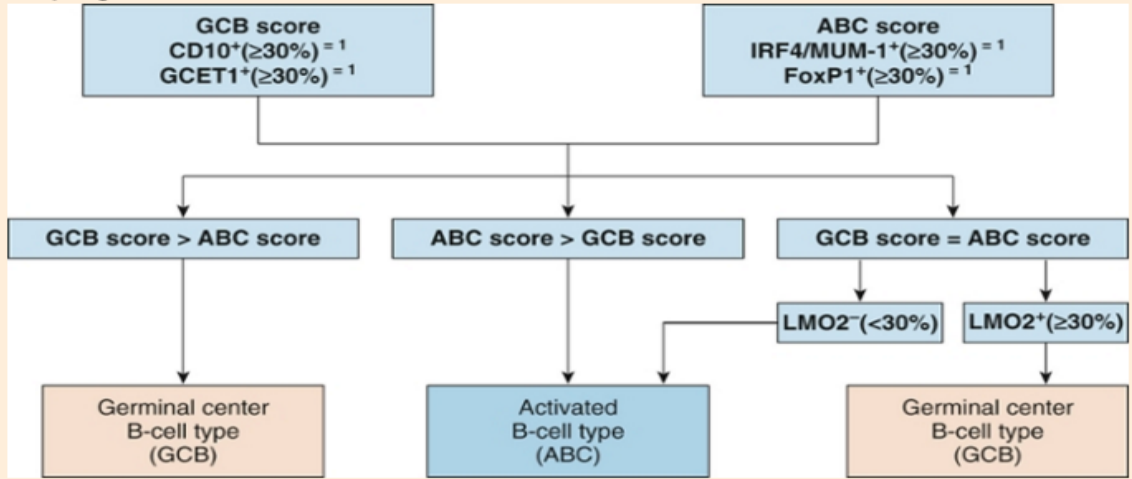
Hans Algorithm¹⁸⁷

CD10 ⁺ (≥30%)	CD10 ⁻ (<30%)		
	BCL6 ⁺ (≥30%) IRF4/MUM-1 ⁻ (<30%)	BCL6 ⁺ (≥30%) IRF4/MUM-1 ⁺ (≥30%)	BCL6 ⁻ (<30%)
Germinal-center B-cell type (GCB)	Non-germinal-center B-cell type (non-GCB)		

Choi Algorithm¹⁸⁸

GCET1 ⁻ (<80%)		GCET1 ⁺ (≥80%)	
CD10 ⁺ (≥30%)	CD10 ⁻ (<30%)		IRF4/MUM-1 ⁺ (≥80%)
	BCL6 ⁺ (≥30%) FoxP1 ⁻ (<80%)	BCL6 ⁻ (<30%) FoxP1 ⁺ (≥80%)	
Germinal-center B-cell type (GCB)	Activated B-cell type (ABC)		Germinal-center B-cell type (GCB)

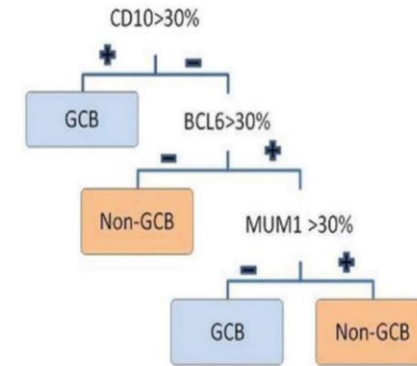
Tally Algorithm¹⁸⁹



Visco-Young Algorithm¹⁹⁰

CD10 ⁺ (≥30%)	CD10 ⁻ (<30%)		
	BCL6 ⁺ (≥30%) FoxP1 ⁻ (<60%)	BCL6 ⁻ (<30%) FoxP1 ⁻ (<60%)	FoxP1 ⁺ (≥60%)
Germinal-center B-cell type (GCB)	Non-germinal-center B-cell type (non-GCB)		

DLBCL NOS



Hans algorithm : CD10, BCL6 and IRF4/MUM1

Germinal center B-cell type
Activated B-cell type

Germinal merkez B-hücre benzeri (GMB)	Aktive B hücre benzeri (ABH)
Daha iyi prognoz	Daha kötü prognoz
Beş yıllık sağkalım: %76	Beş yıllık sağkalım: %34
	İmmünoblastik↑
12q12 kromozom kazancı	3q, 18q21-22 kromozom kazançları 6q21-q22 kromozom kaybı
<ul style="list-style-type: none">▪ BCL2 translokasyonları▪ MYC translokasyonları▪ EZH2 mutasyonu▪ PTEN delesyonu	<ul style="list-style-type: none">▪ NF-κB yolağının aktivasyonu▪ CARD11 mutasyonu▪ CD79B mutasyonu▪ TNFAIP3 mutasyonu▪ MYD88 mutasyonu

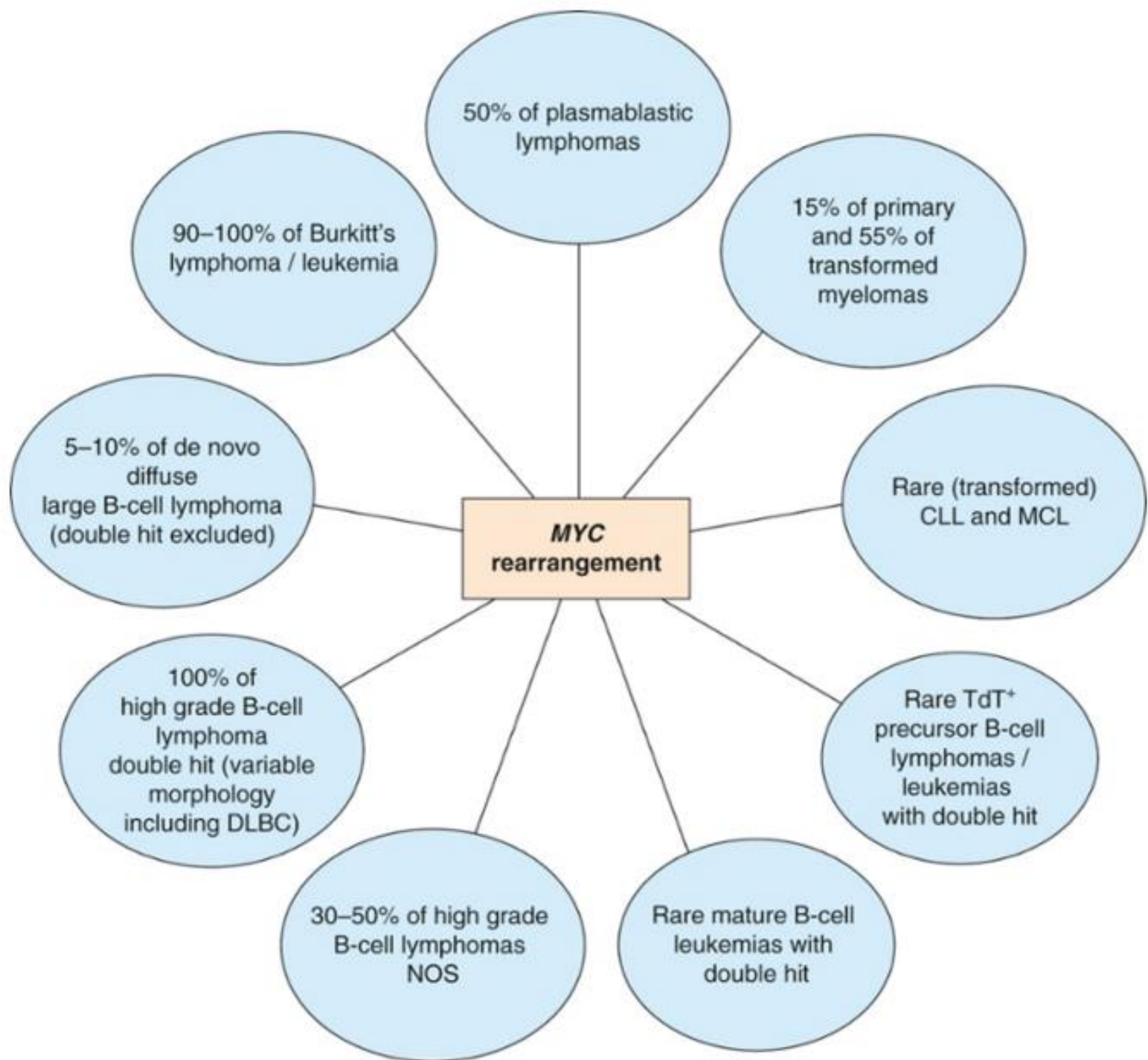
Değişen nedir???

- NGS
- Yeni klinik, patolojik, genetik/moleküler data
- Ortak multisentrik çalışmalar

The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms

Steven H. Swerdlow, Elias Campo, Stefano A. Pileri, Nancy Lee Harris, Harald Stein, Reiner Siebert, Ranjana Advani, Michele Ghielmini, Gilles A. Salles, Andrew D. Zelenetz and Elaine S. Jaffe

Diffuse large B-cell lymphoma, NOS	- Distinction of GCB vs ABC/non-GC type required with use of immunohistochemical algorithm acceptable, may affect therapy.
	- Coexpression of MYC and BCL2 considered new prognostic marker (double-expressor lymphoma).
	- Mutational landscape better understood but clinical impact remains to be determined.
EBV ⁺ DLBCL, NOS	- This term replaces EBV ⁺ DLBCL of the elderly because it may occur in younger patients.
	- Does not include EBV ⁺ B-cell lymphomas that can be given a more specific diagnosis.
EBV ⁺ mucocutaneous ulcer	- Newly recognized entity associated with iatrogenic immunosuppression or age-related immunosenescence.
Burkitt lymphoma	- <i>TCF3</i> or <i>ID3</i> mutations in up to ~70% of cases.
Burkitt-like lymphoma with 11q aberration	- New provisional entity that closely resembles Burkitt lymphoma but lacks <i>MYC</i> rearrangement and has some other distinctive features.
High-grade B-cell lymphoma, NOS	- Together with the new category for the "double-/triple-hit" lymphomas, replaces the 2008 category of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BCLU).
	- Includes blastoid-appearing large B-cell lymphomas and cases lacking <i>MYC</i> and <i>BCL2</i> or <i>BCL6</i> translocations that would formerly have been called BCLU.



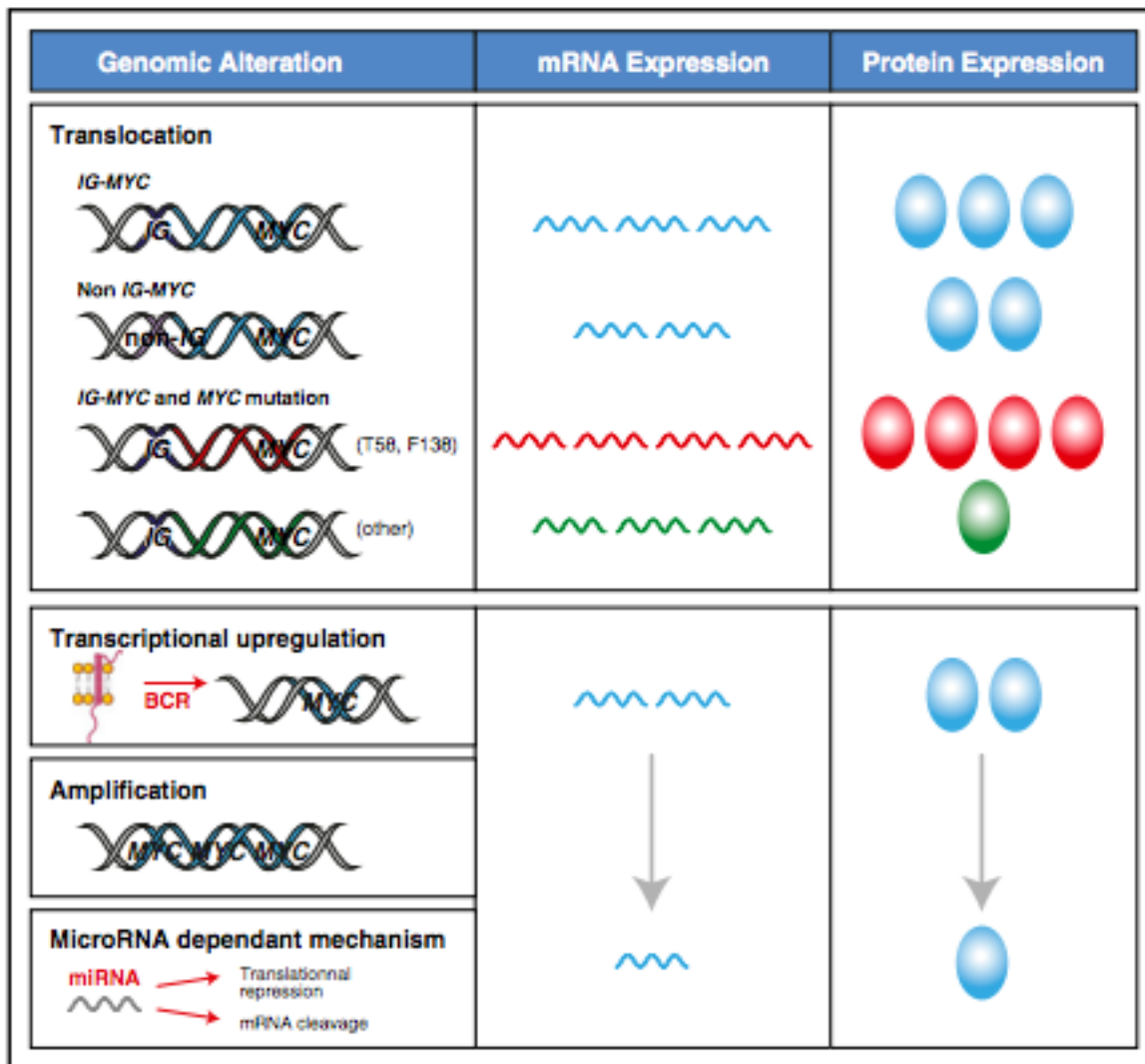


Figure 1. Mechanisms of *MYC* deregulation in aggressive lymphomas. The levels of *MYC* mRNA expression and protein can vary according to the mechanism that is driving transcription and the presence of *MYC* mutations, which are reflected as different colors for mRNA and protein (blue for wild type). *MYC* mRNA is the highest in the context of an *IG-MYC* translocation. Decreased mRNA degradation in patients who have *MYC* T58 mutations (red) can further increase *MYC* mRNA levels, whereas other mutations can decrease *MYC* protein levels (green). *MYC* transcription can be increased through mechanisms other than translocations, but they are more variable and generally result in lower *MYC* protein expression.

Approach to the diagnosis and treatment of high-grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements .Pierre Sesques and Nathalie A. Johnson Blood 2017 129:280-288

WHO 2016 DBBHL alt grupları ve tipleri

DBBHL, NOS(Not Otherwise Specified)

- **Morfolojik varyantları**
- **sentroblastik**
- **immunoblastik**
- **anaplastic**
- **nadir tipler**

- **Moleküler subtipler**
 - **Germinal merkez B hücre-benzeri (GCB)**
 - **Activated B hücre tipi (ABC)**

Büyük B Hücreli Lenfomanın diğer tipleri

- **T hücre/histositten zengin büyük B hücreli lenfoma**
- **Primer SSS DBBHL**
- **EBV⁺ DBBHL, NOS**
- **IRF4 rearrangementli DBBHL (provisional entity)**
- **Primer mediastinal (timik) büyük B hücreli lenfoma**
- **Intravasküler büyük B hücreli lenfoma**
- **Kronik inflamasyonun eşlik ettiği DBBHL**
- **Lenfomatoid granulomatosis**
- **ALK⁺ büyük B hücreli lenfoma**
- **Plazmablastik lenfoma**
- **HHV8⁺ difuz büyük B hücreli lenfoma**
- **Primer efüzyon lenfoması**

Yüksek gradeli B Hücreli Lenfoma

- **Yüksek gradeli B Hücreli Lenfoma, myc ve bcl2 ve/veya bcl6 rearrangementlı**
- **Yüksek gradeli B Hücreli Lenfoma, NOS**

B hücreli lenfoma, DBBHL ile klasik Hodgkin lenfoma arası özellikler gösteren

Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Revised 4th. Ed. Lyon, France: IARC Press 2017

Double Ekspresör Lenfoma

- Myc protein ekspresyonu (%30-50)
- Bcl-2 protein ekspresyonu (%20-35)
- Cut-off myc >%40 , bcl-2>%50
- Bu lenfomaların çoğu myc/bcl-2 kromozomal alterasyonlar taşımazlar
- Kötü prognoz> DBBHL, NOS.

DBBHL, NOS için prognostik faktördür, farklı kategori değildir

High grade B cell lymphoma, with rearrangements of myc and bcl2 and/or bcl6

Yüksek gradeli B hücreli lenfoma, myc ve bcl2 ve/veya bcl6 rearrangementlı

- %5-15 DBBHL, NOS
- Yüksek proliferasyon indeksli, yıldızlı gök görüntüsüne sahip (BL-benzeri) fakat birden fazla belirgin nukleoluslu ve düzensiz sınırlı büyük çekirdekli (DBBHL-benzeri)



The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Steven H. Swerdlow, et al. Blood 2016 127:2375-2390

WHO 2016

1-Yüksek gradeli B hücreli lenfoma, myc ve bcl-2 ve/veya bcl6 rear. izlenen

2-Yüksek gradeli B hücreli lenfoma, NOS

'WHO 2008/ Unclassified B hücreli lenfoma ile Burkitt lenfoma arası özellikler içeren'

Klinik olarak: spesifik klinik prezantasyonları yok

yaşlı, güçsüz

İleri evre prezentasyonlu

Evre III-IV, kemik iliği tutulumu+, CNN tutulumu

sık

Extranodal alan tutulumu>1

Yüksek LDH

Yüksek IPI skoru

- Yüksek Gradelı B hücreli Lenfoma/ primer; ½ vakada eş zamanlı ya da öncesinde FL
 - Double hit: myc+bcl2 rearr.
 - Triple lenfoma; myc+bcl-2+bcl6 rear.+
 - Myc ve bcl-6 rear.+ vakalar :ABC fenotip/IRF4+
 - Klinik davranış triple=DH-DBBHL benzer

 - Myc rearr. IHK ile saptamak zor
 - Myc rear. Partnerleri IG veya non-IG/myc
 - t(8;9)(q23;p13) / PAX5
 - t(3;8)(q27;q24) /bcl6
- non-IG; myc prognoz rölatif olarak t(8;14) iyi

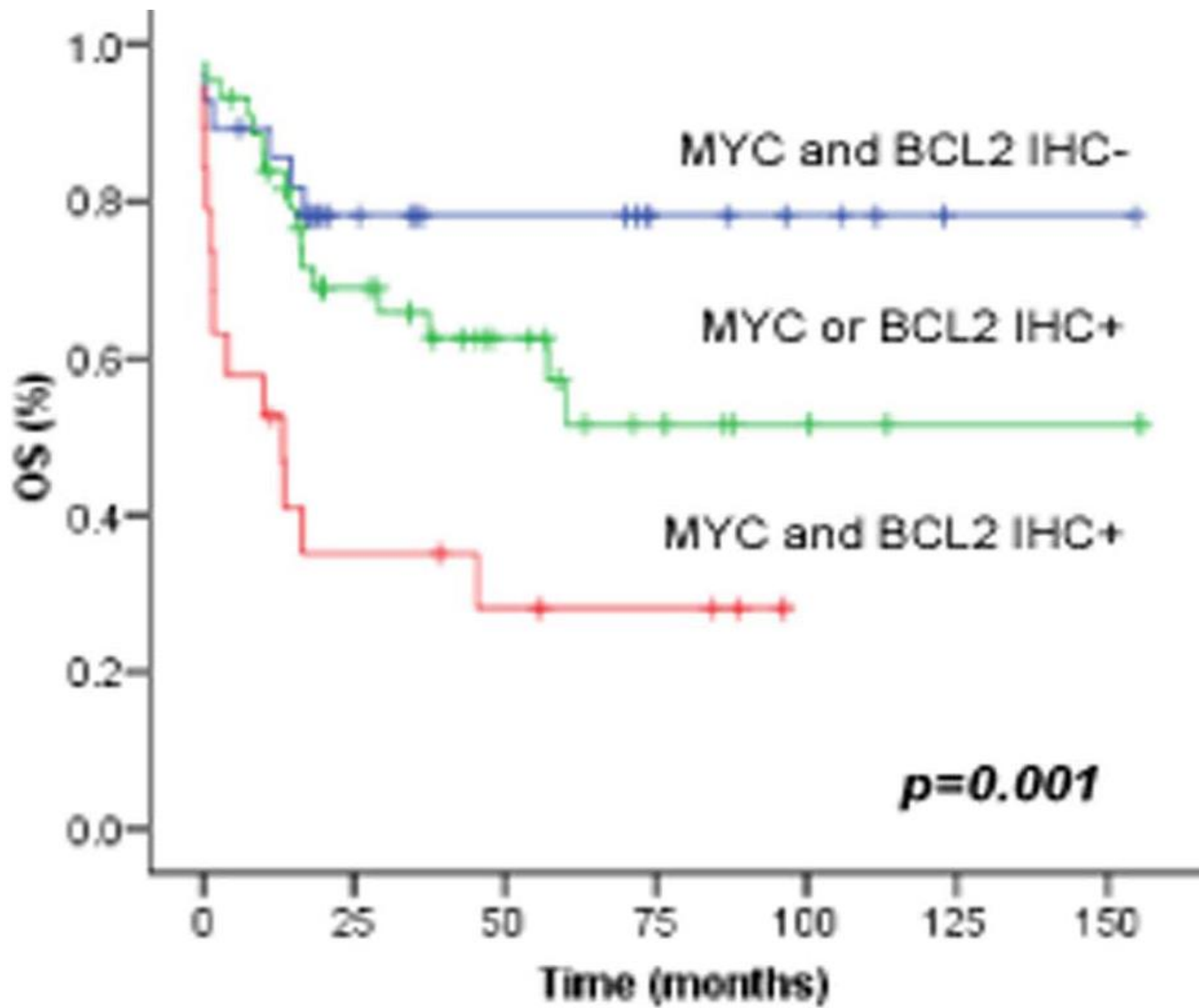
- Myc rearrangementinin tek başına prognozla ilişkisi???
- Amplifikasyon ve duplikasyonların klinik önemi bilinmiyor???

NGS çalışmaları ile DBBHL alt gruplarında çeşitli somatik mutasyonları tespit edildi

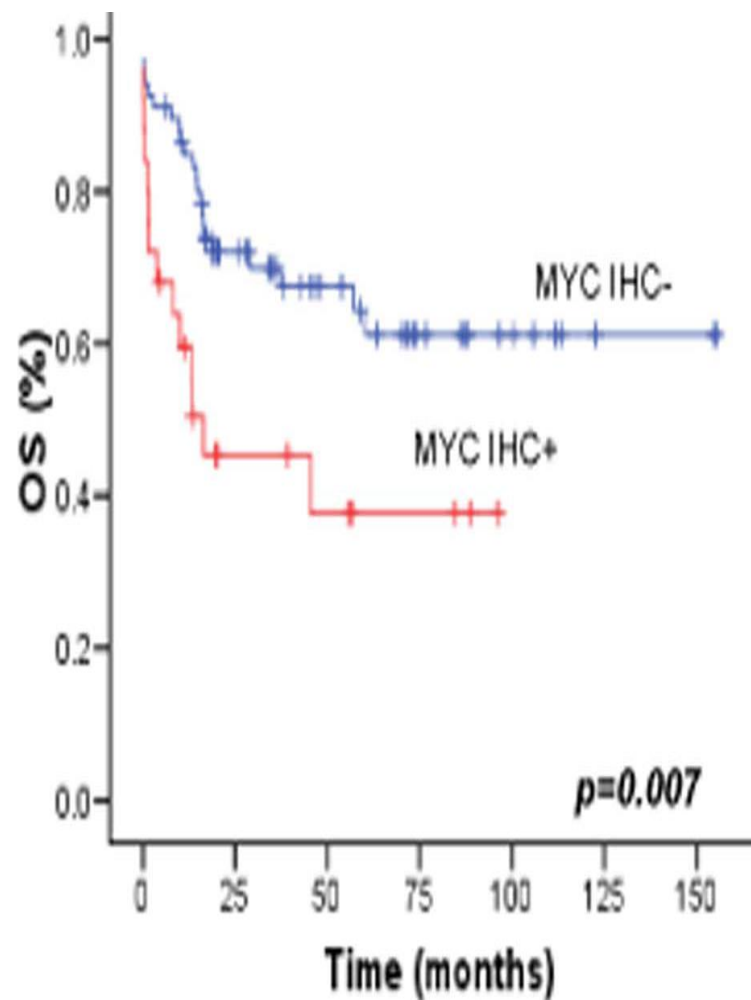
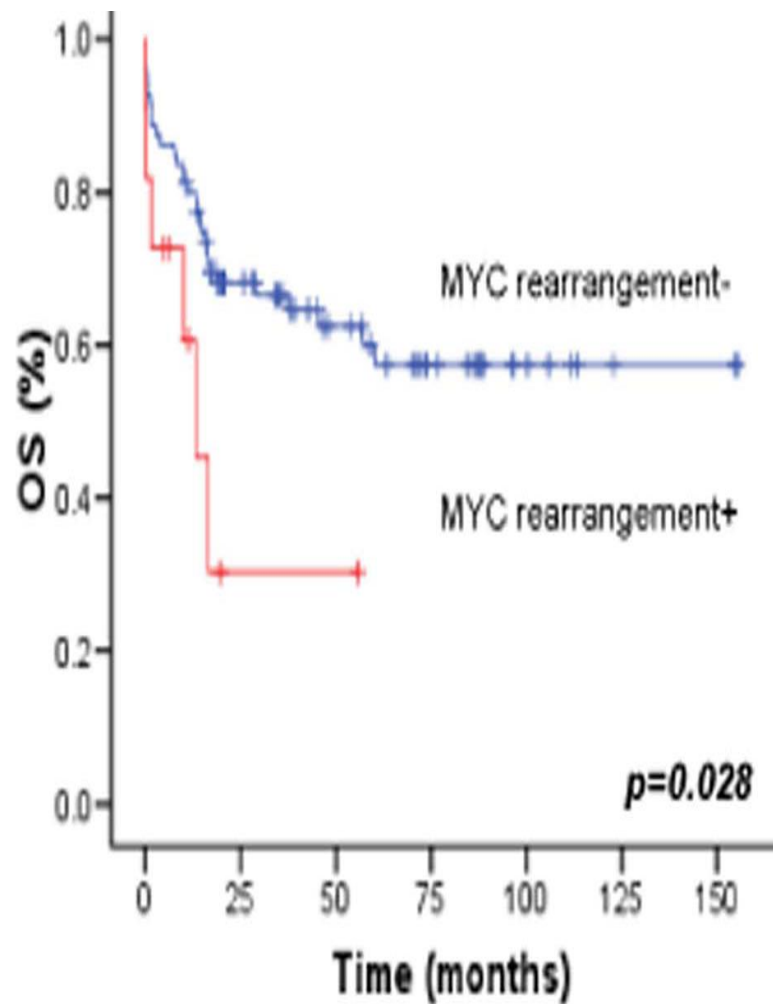
- TP53'in inaktivasyon mutasyonları
- Immunsurveillance tutan genler
- Epigenetik regülatördeki değişiklikler

- DBBHL-GCB; EZH2 histon metil transferaz, bcl2 translokasyonları ve GNA13 hücre motilite regülatör genlerinde mutasyonlar
- DBBHL-ABC; MYD88, CD79A, CARD11, TNFAIP3(B hücre aktivatör reseptör) gen mutasyonları ve NFkB yol genlerinde mutasyonlar

- DBBHL/DH-TH, standart KT
(rituximab+cyclophosphamide+doxorubicine+vincristine+prednisone: R-CHOP) yanıt suboptimal
- Etoposide+prednisone+vincristine+cyclophosphamide+doxorubicine+rituximab:EPOCH-R prognoz daha iyi



Bellas C ve ark. PLOS ONE 2014;9:1-9



Bellas C ve ark. PLOS ONE 2014;9:1-9

Poor Prognostic Indicators in Diffuse Large B-Cell Lymphoma

Clinical

- High IPI score*

Morphologic

- Immunoblastic or plasmablastic morphology

Immunohistochemical

- Lack of germinal-center cell phenotype (CD10⁻, BCL6⁻, LMO2⁻, or following various cell-of-origin algorithms)*
- Double expression of MYC and BCL2*
- CD5 expression
- High proliferation (Ki67) index (controversial)
- Lack of CD30 expression
- CD43 expression
- IRF4/MUM-1 expression
- P53 expression
- CD44s expression
- P14 (ARF) nuclear overexpression
- Cyclin D3 expression in ≥50% of lymphoma cells
- Cyclin D2 expression

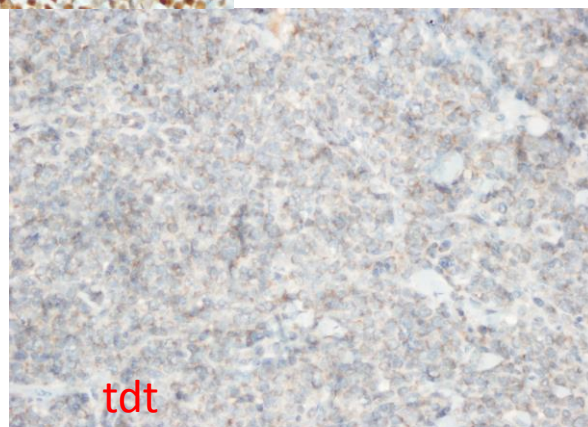
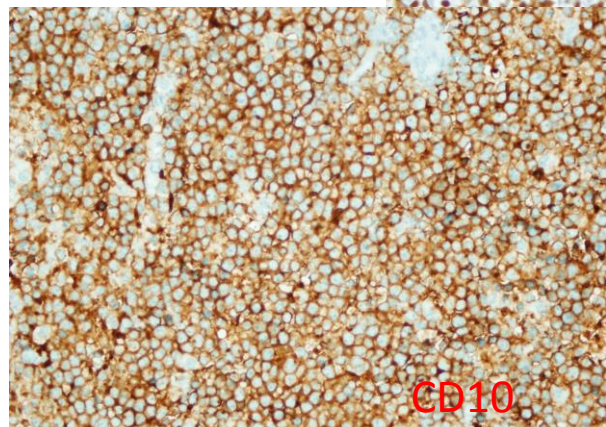
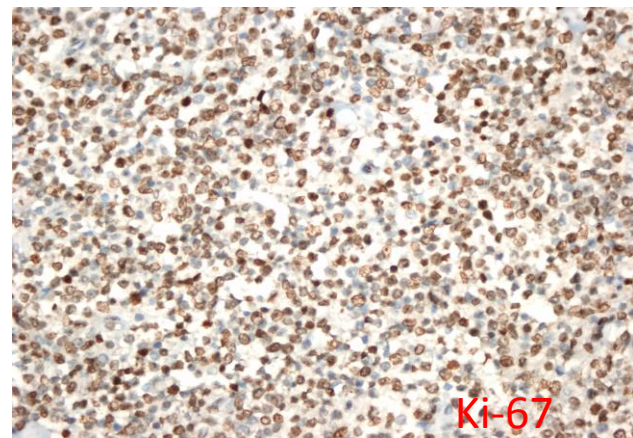
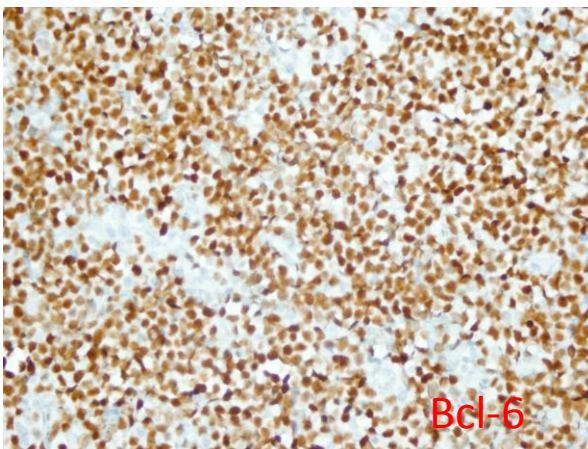
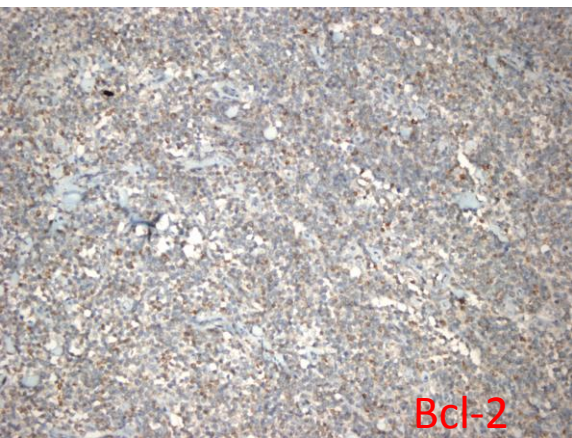
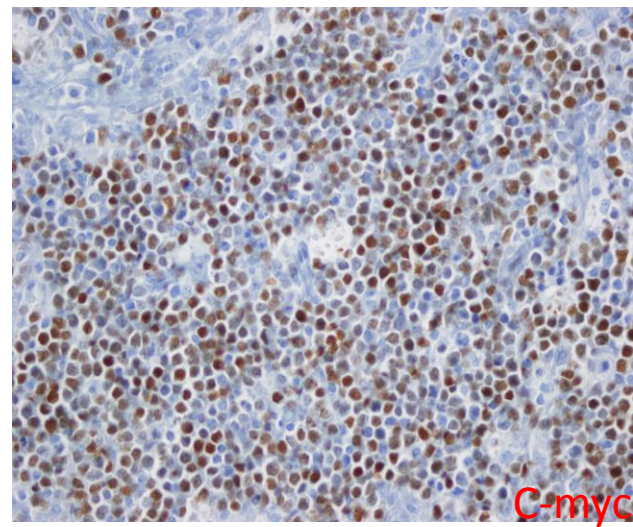
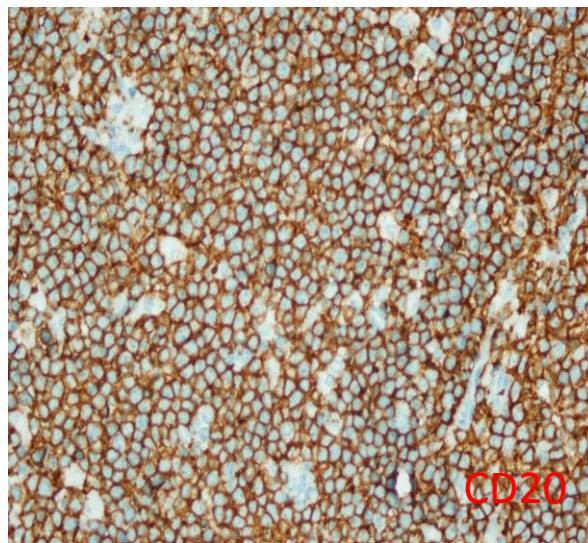
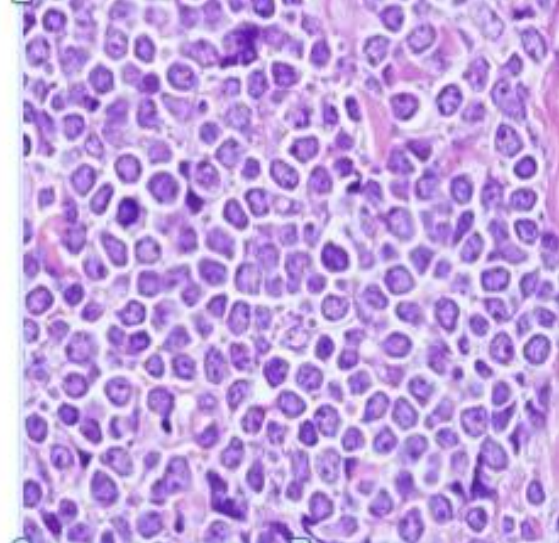
- Lung-resistance protein expression
- Survivin expression
- Caspase 9 inhibition profile
- Lack of HLA-DR expression
- Poor tumor-infiltrating T-cell response, especially CD4⁺ or FOXP3⁺ T cells
- High numbers of granzyme B⁺ or TIA-1⁺ tumor-infiltrating T cells
- Lack of SPARC⁺ stromal cells (for ABC subgroup)

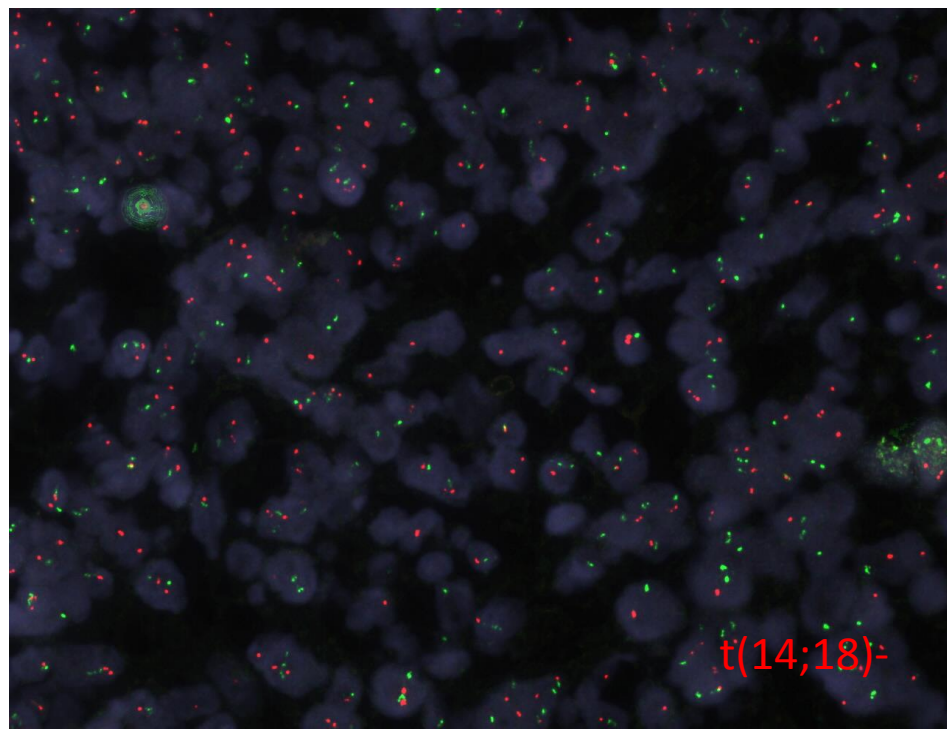
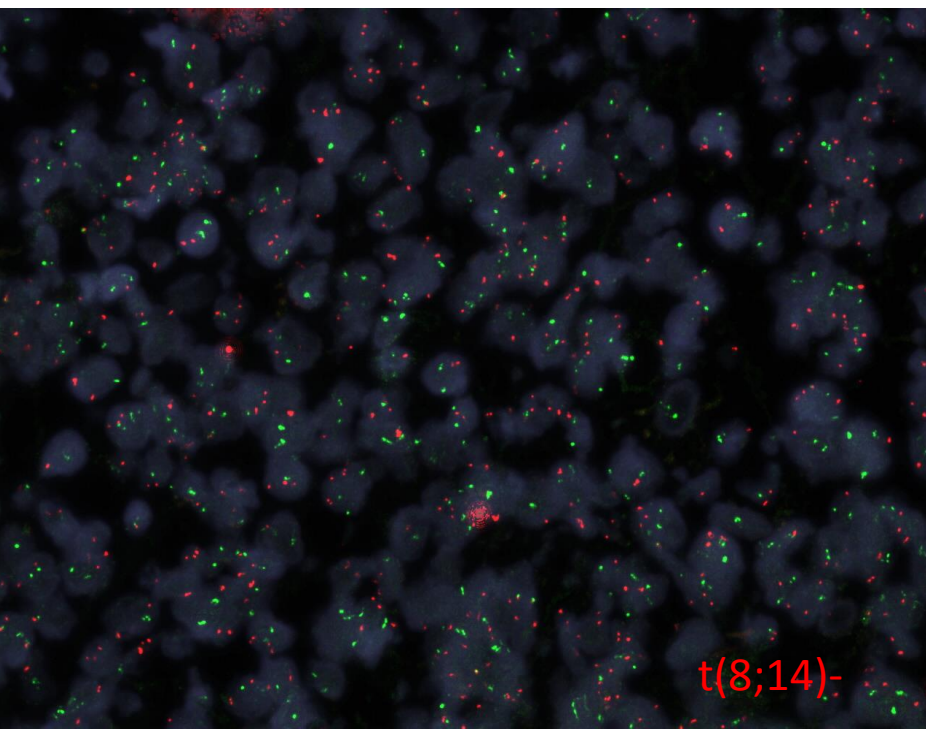
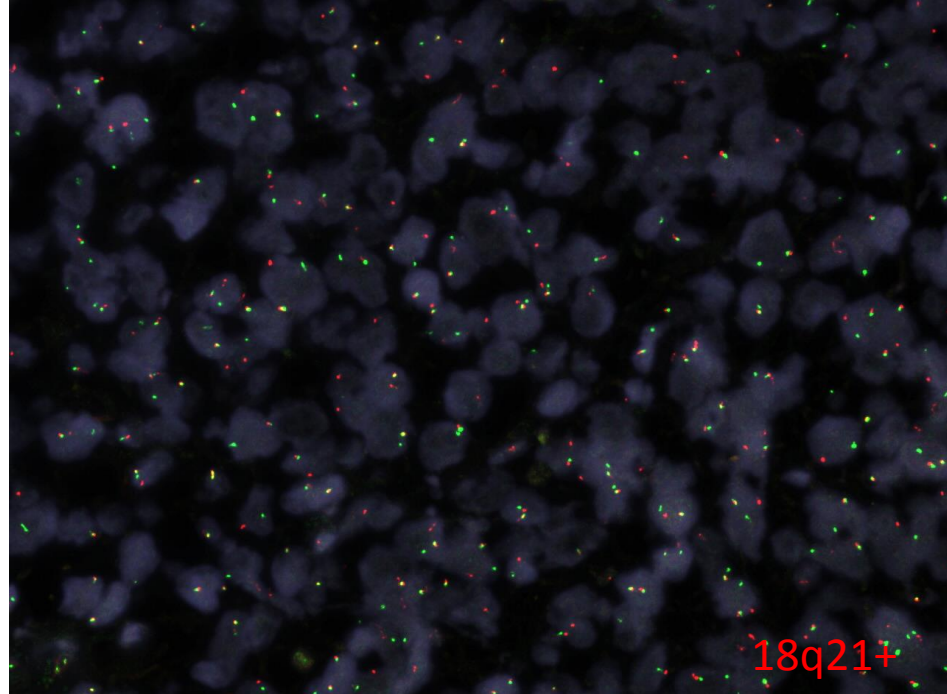
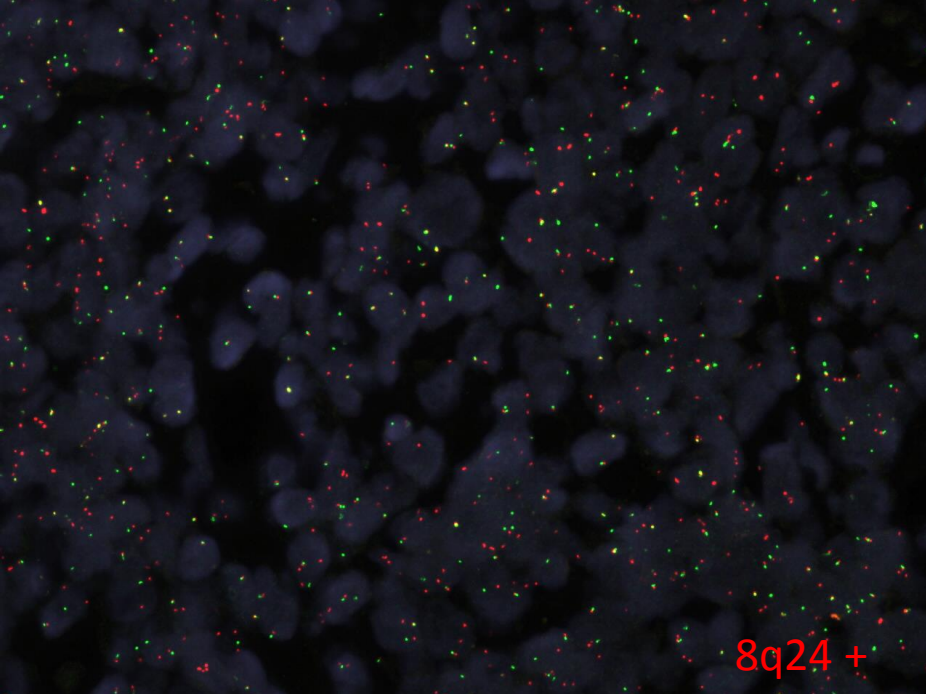
Molecular

- ABC type on gene-expression profiling*
- Low HGAL expression
- Low LMO2 expression
- Redox signature score
- *BCL2* gene rearrangement
- Lack of *BCL6* gene rearrangement
- Lack of *BCL6* gene mutation
- Low level of *BCL6* messenger RNA transcripts
- Non-IG/*BCL6* fusion
- *MYC* gene rearrangement, especially IG/*MYC*
Gain or increased copy number of *MYC*
- *TP53* mutation
- Lack of hypermethylation of O⁶-methylguanine DNA methyltransferase promoter
- Gains involving chromosome region 3p11-p12

Vaka1

- 60y/K
- Karın ağrısı, ateş, halsizlik
- Batın USG: sağ alt kadranda 13x7cm mezenterik yağlı planları ve lenf düğümlerini tutan kitle
- Hemogram anemi +, LDH(y)
- Kitleden bx





IHK sonuçları

- CD20+
- CD10+
- Bcl-6+
- Bcl2+
- C-myc+
- CD5-
- Mum1-
- Tdt-
- Siklin D1-
- Ki-67 %80-90
- GCB

FISH sonuçları

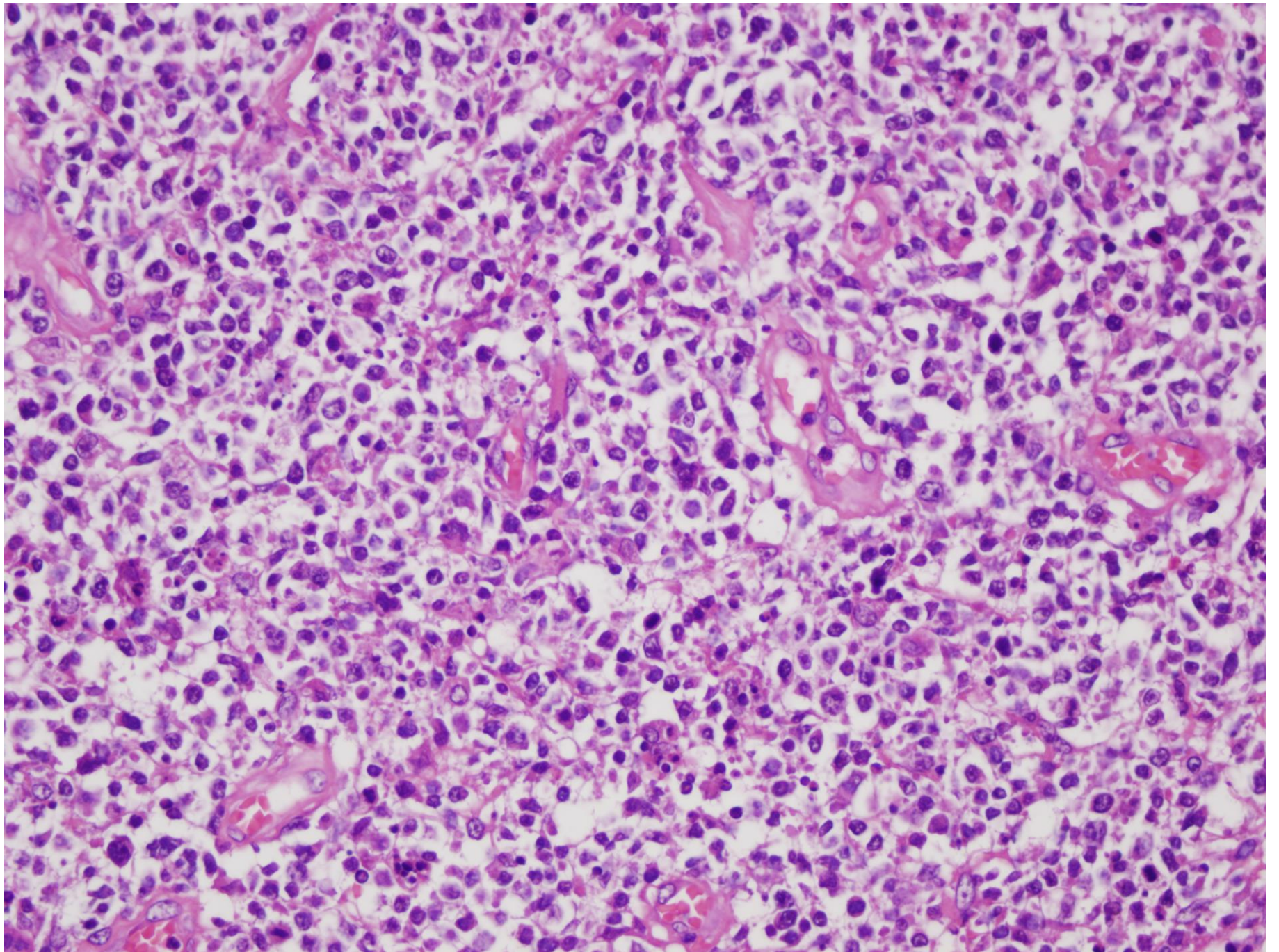
- 8q24 rearr.(+)
- 18q21 rearr.(+)
- t(8:14)(q24;q32) (-)
- t(14;18)(q32;q21) (-)
- 3q27 rearr (-)

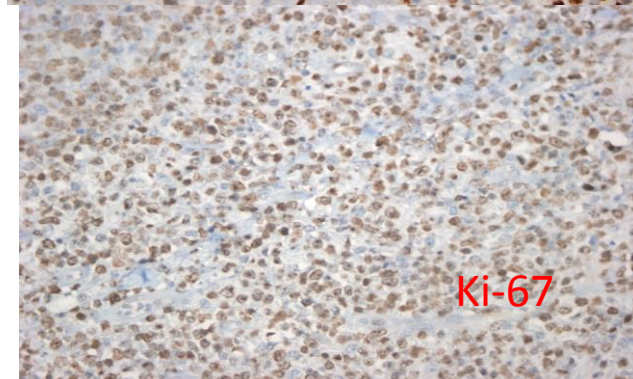
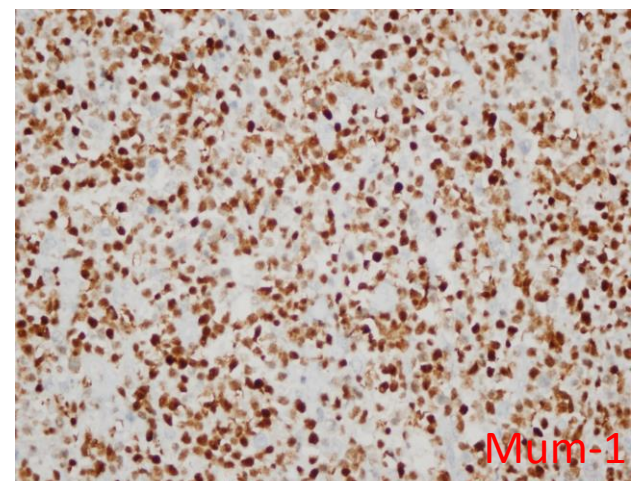
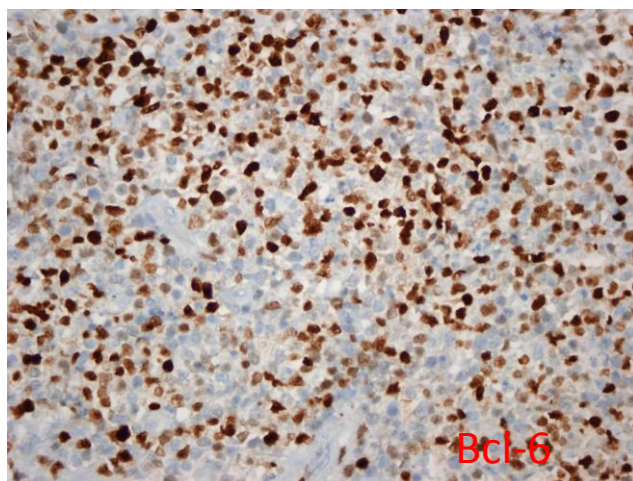
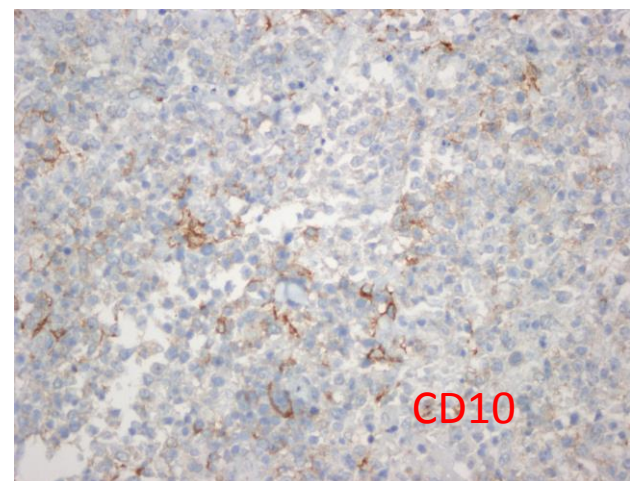
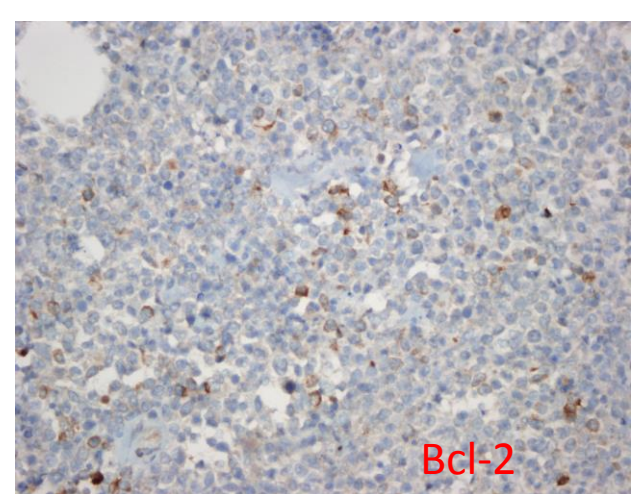
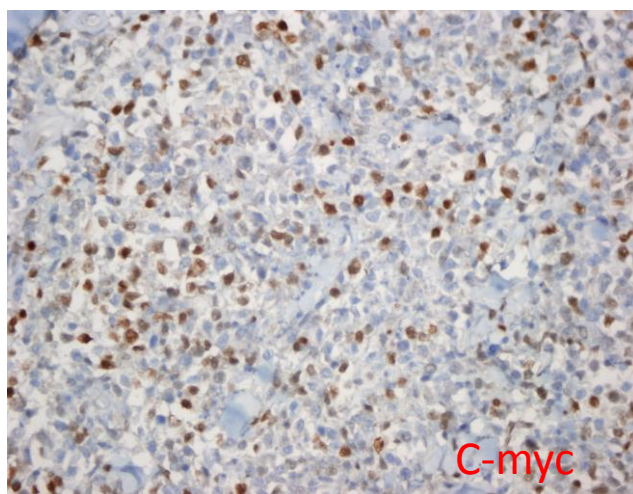
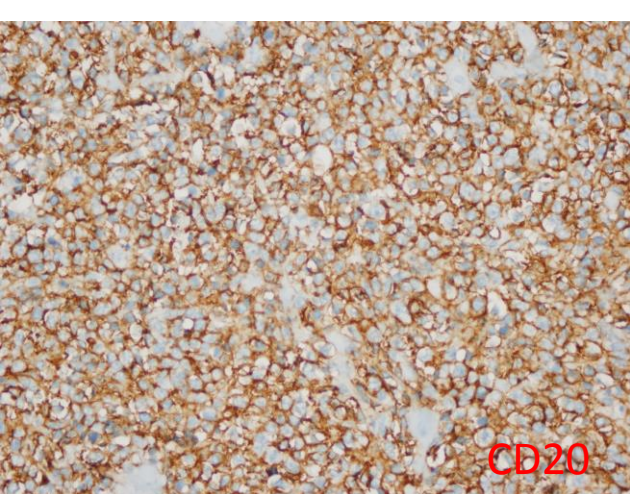
Patolojik Tanı

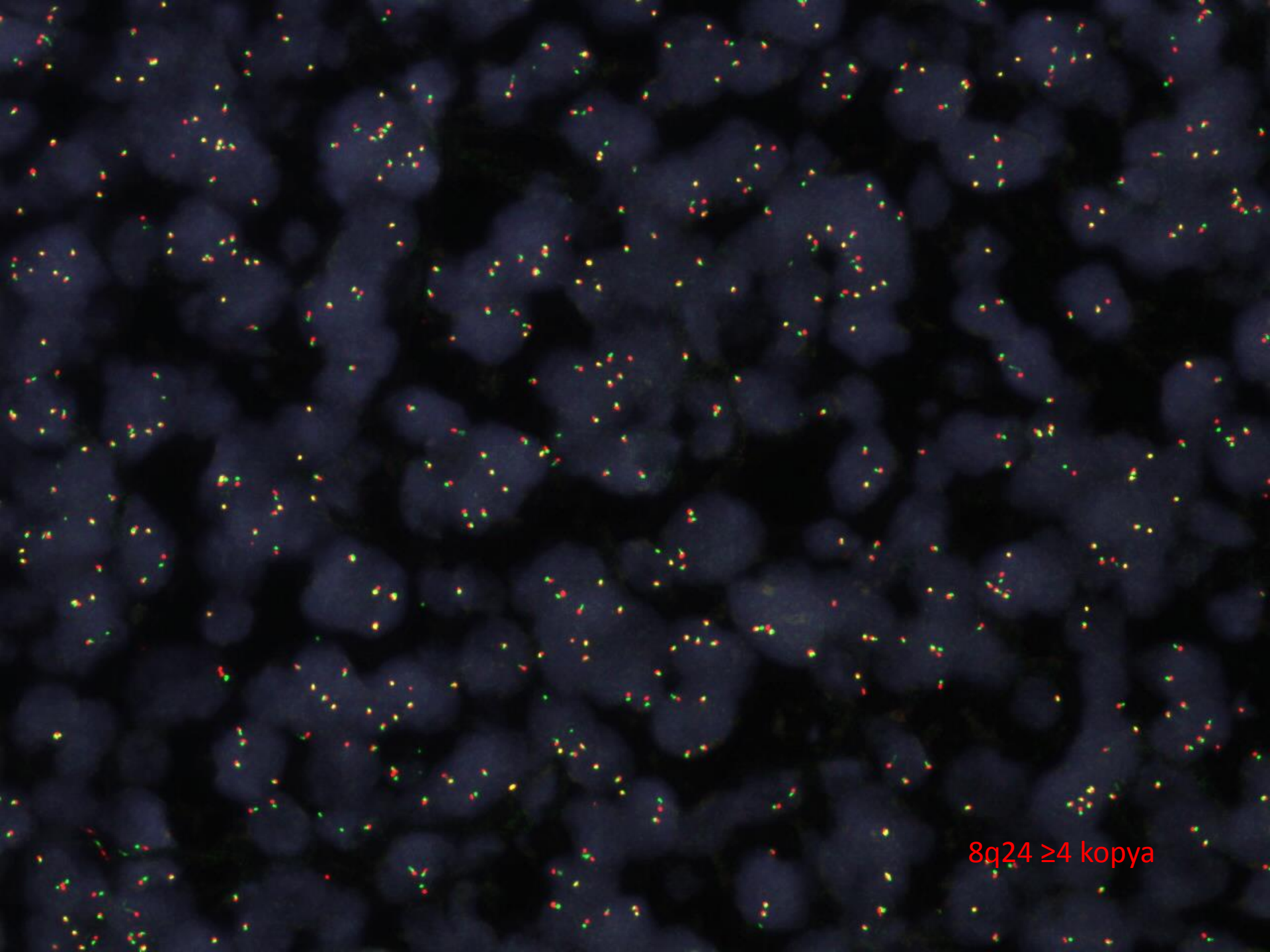
- DBBHL,NOS. Germinal merkez benzeri(GCB-like) fenotip, myc ve bcl-2 ekspresyonlu (double ekspresör)
- Immunhistokimya sonuçları: c-myc+, Bcl-2+ ekspresyonu
- FISH sonuçları:
 - 8q24 ve 18q21 bölge rearrangementı (+)
 - t(8;14)(q24;q32), t(14;18)(q32;q21) ve 3q27 bölge rearr (-)
- **Yüksek gradeli B Hücreli Lenfoma, myc ve bcl-2 rearrangementlı (Double hit)**

Vaka 2

- 63y/E
- Sol inguinal bölgede kitle-dış merkezde BL tanılı
- B semptom+
- F.muayenede sağ ve sol bilateral inguinal kitle
- PET: bilateral servikal , mediastinal, abdominal , bilateral inguinal FDG tutulumları
- Hemogram anemi, ESR ve LDH(y)
- ingunal bölgeden bx







8q24 \geq 4 kopya

- IHK sonuçları
- CD20+
- CD10 soluk+
- Bcl-6+
- Mum-1+
- Bcl-2 seyrek+
- C-myc+
- Ki-67 %70-80
- GCB

- FISH sonuçları
- 8q24 rear. (-)
- t(8;14)(q24;q32) (-)
- 18q21 rear. (-)
- t(14;18)(q32;q21) (-)
- 3q27 rear.(-)
- 8q24 bölgesinde amplifikasyon***

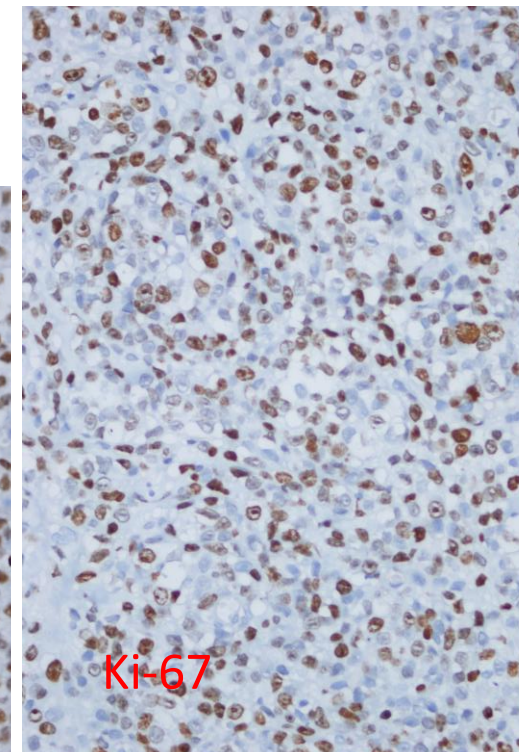
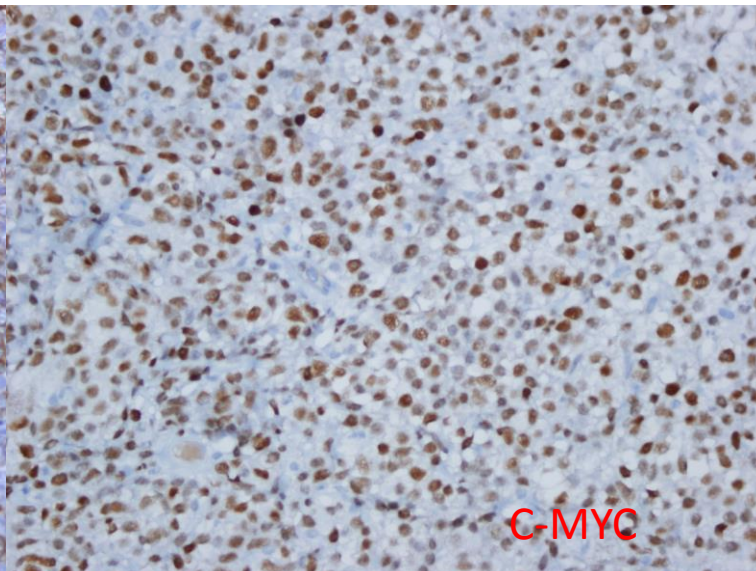
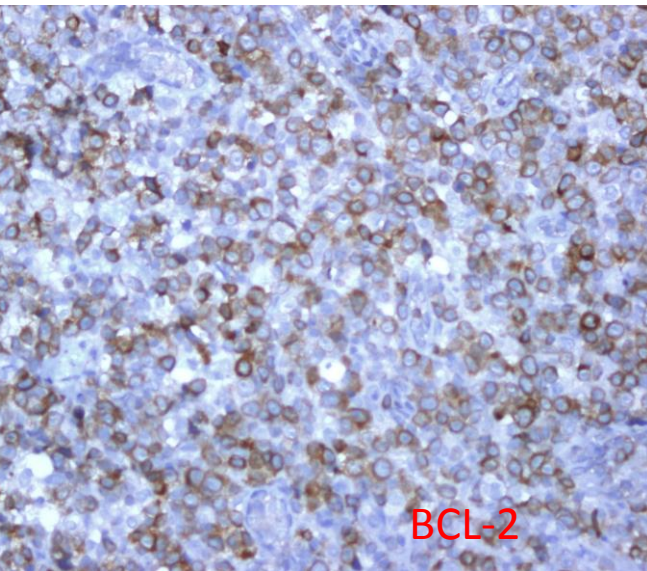
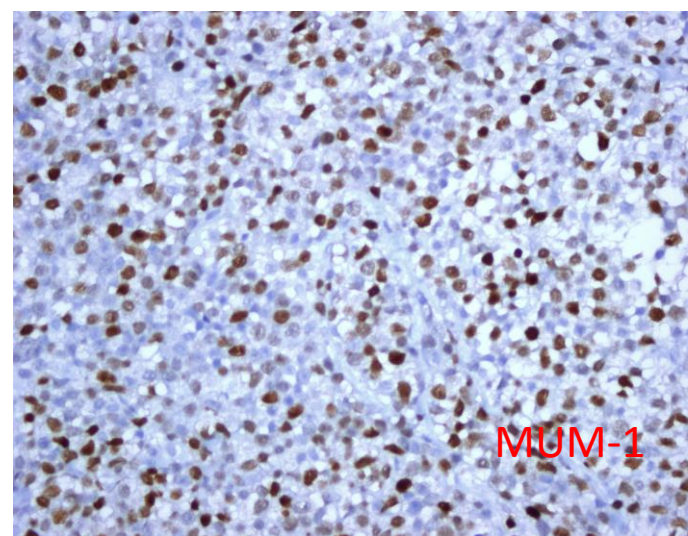
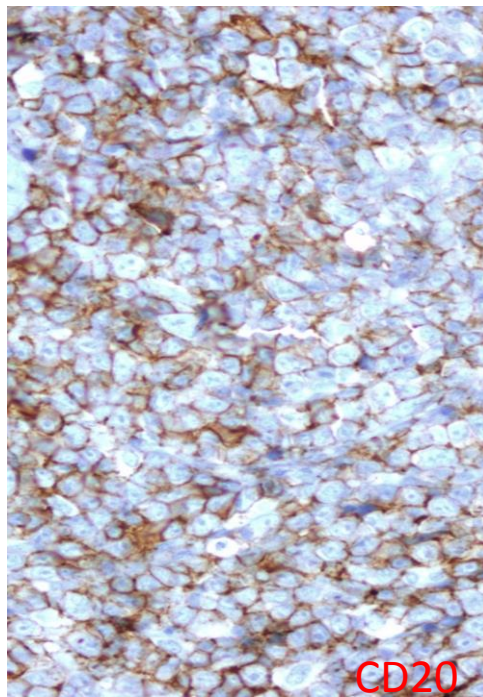
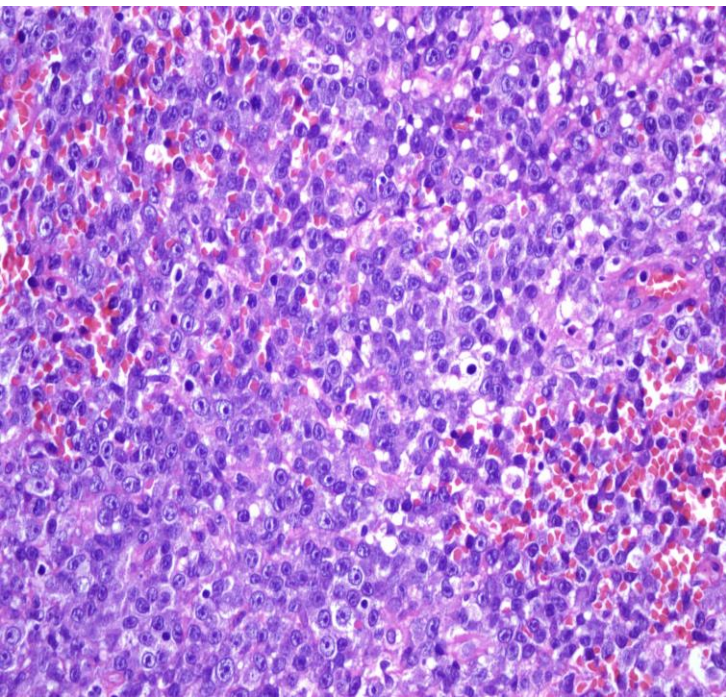
Patolojik tanı

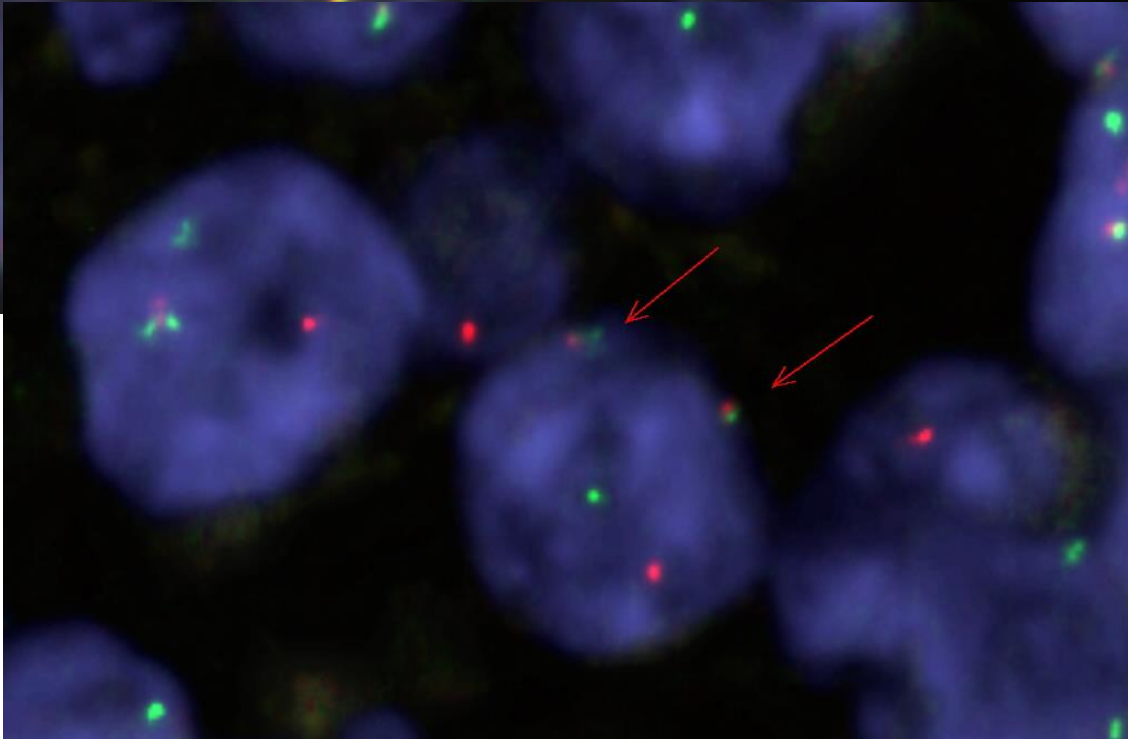
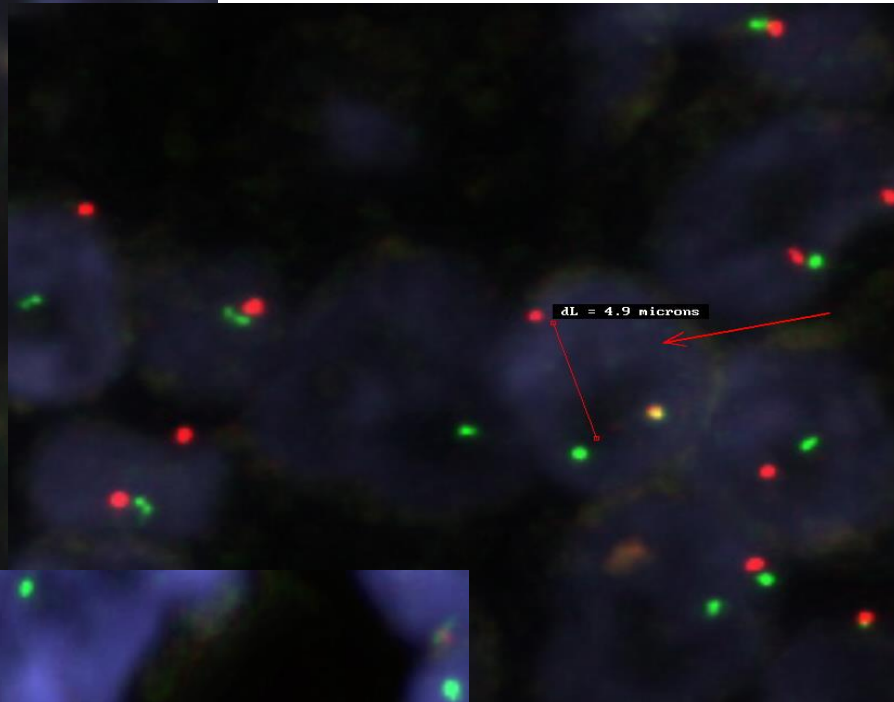
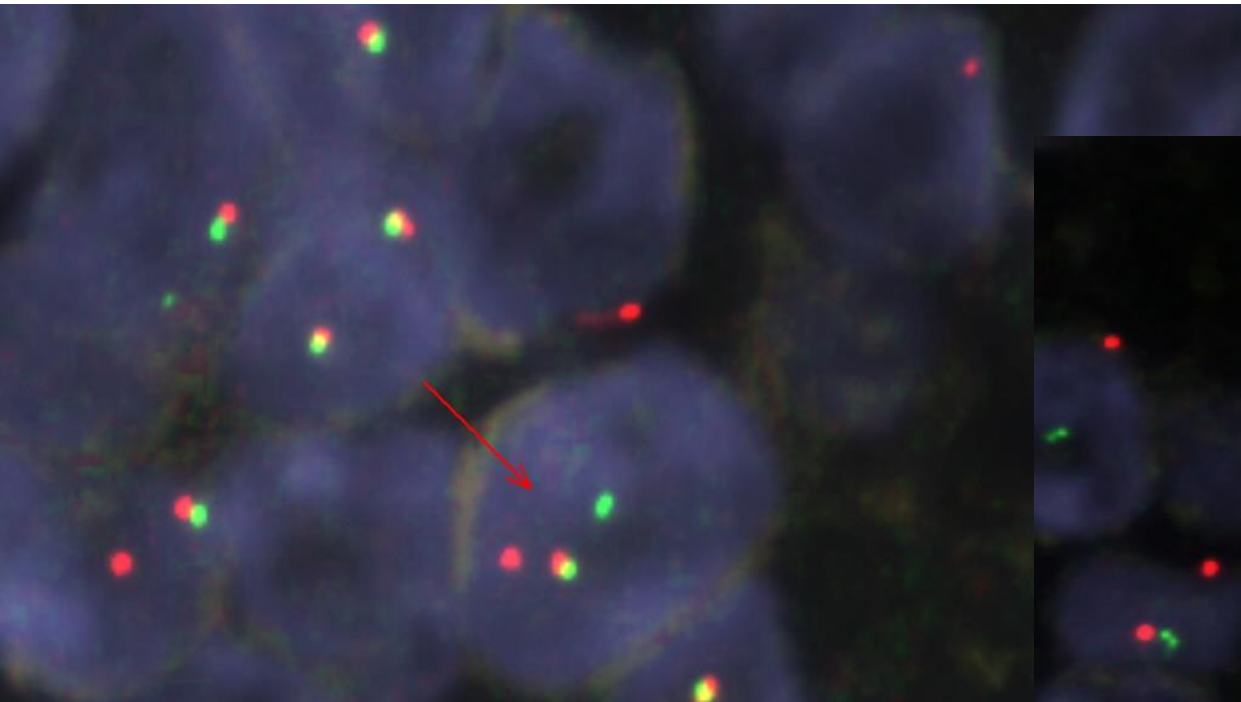
- DBBHL, NOS. Germinal merkez benzeri(GCB) fenotip
 - İmmunhistokimya sonuçları: c-myc(+), bcl-2(-)
- FISH sonuçları:
- 8q24 bölgesinde amplifikasyon
 - 8q24, 18q21 ve 3q27 bölge rearrangement(-)

Vaka 3

- 46 y/K
- 2008 yılından itibaren poliartrit nedeniyle romatolojinin takibinde, MTX kullanımı var
- Memede 3 aydır hızlı büyüyen kitle mevcut
- Batın US: kc: grade 1 hepatosteatoz, sm(-), LAM(-)
- Meme MR: sol meme ÜDK'da santrali nekrozlu, düzensiz spiküle sınırlı, 57.5mm çapında kitle, buna komşu 19mm çapında ikinci kitle. Sol aksillada en büyüğü 33.5mm LAM'lar

- Kitleden yapılan İİAB: atipik hücreler (Dış merkez)
- Hemogram: WBC: 5000, Hb: 11.7, MCV:79, PLT: 215000
- Kitleden bx





8q24

t(8;14)(q24;q32)

IHK sonuçları

- CD20(+)
- MUM1(+)
- CD10(-),
- Bcl6(-),
- Bcl-2(+),
- c-myc(+)
- CD30(-)
- CD23(-), SiklinD1(-)
- Ki67: %70-80
- ABC

FISH sonuçları

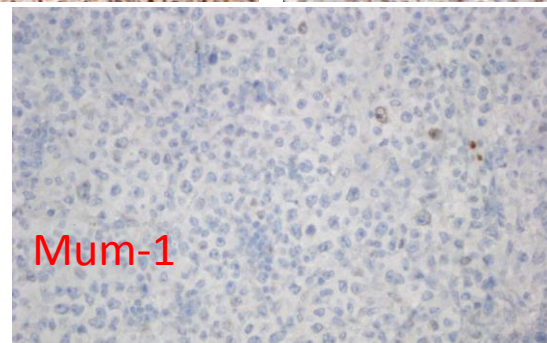
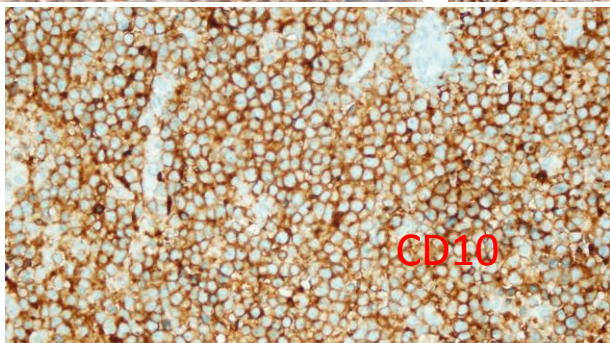
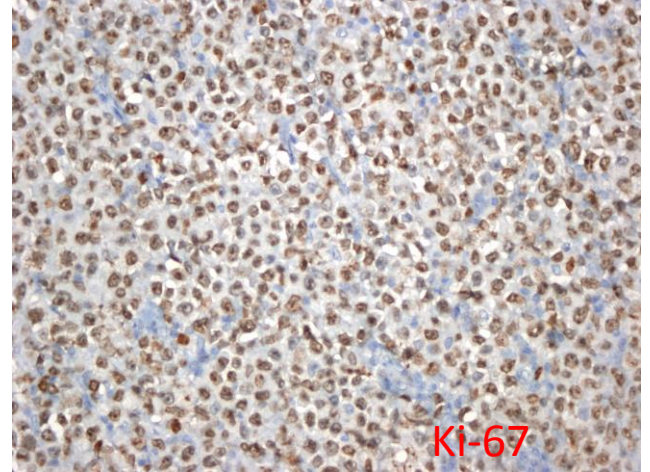
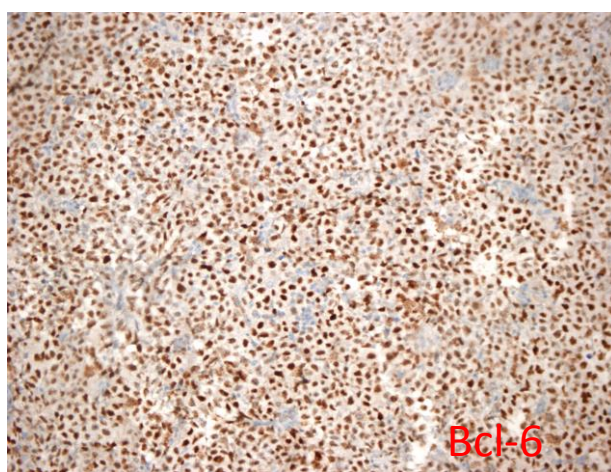
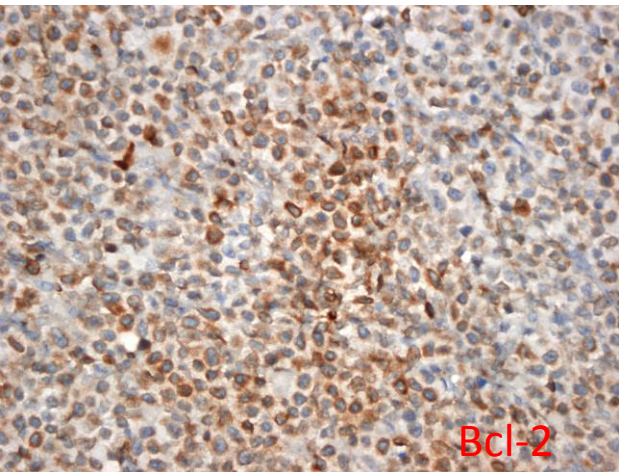
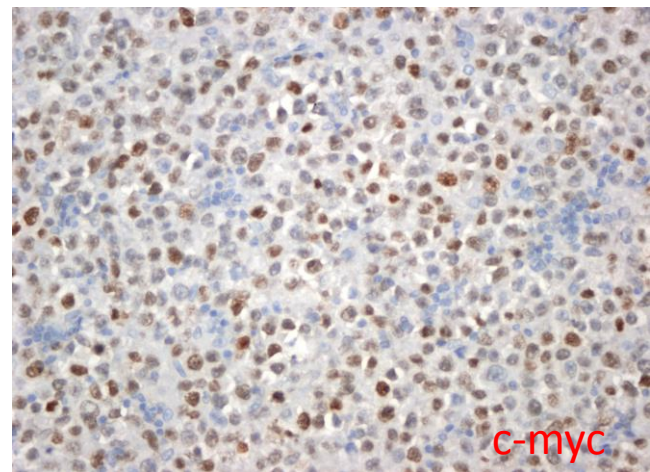
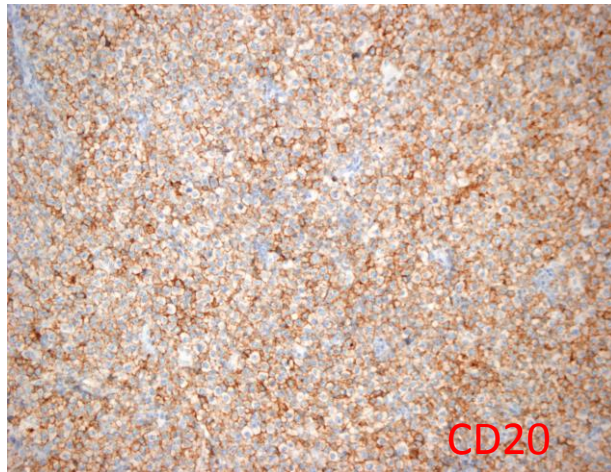
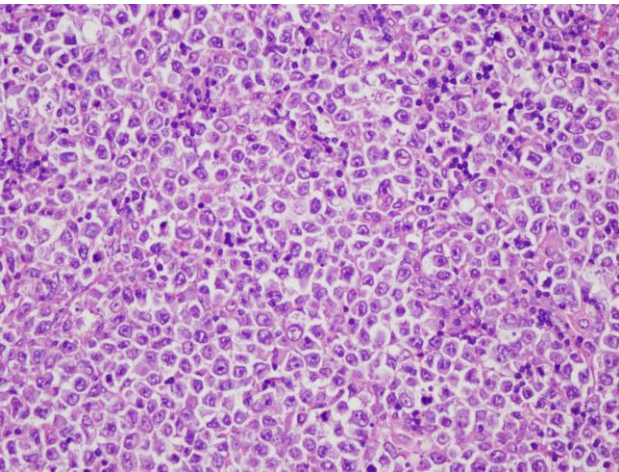
- 8q24 rearr. : (+)
- t(8;14)(q24;q32): (+)
- 18q21 rearr.(-)
- t(14;18)(q32;q21):(-)
- 3q27(Bcl6) rearr.: (-)

Patolojik Tanı

- DBBHL, NOS. Postgerminal merkez benzeri fenotip (ABC-like), myc ve bcl2 ekspresyonlu (double ekspresör)
- İmmunhistokimya sonuçları: c-myc(+), bcl2(+)
- FISH sonuçları:
 - 8q24 bölge rearr. ve t(8;14)(q24;q32)+
 - 18q21 bölge rearr. ve t(14;18)(q32;q21)-
 - 3q27 bölge rearr.-

Vaka 4

- 43y/E
- Karın şişliği, ağrı, sol inguinal bölgede 4cm kitle
- B semptom+
- Hemogram N, LDH (y)
- Inguinal kitle bx



- IHK sonuçları
- CD20+
- CD10+
- Bcl-6+
- c-myc+
- Bcl-2+
- Ki-67 %80-90
- GCB

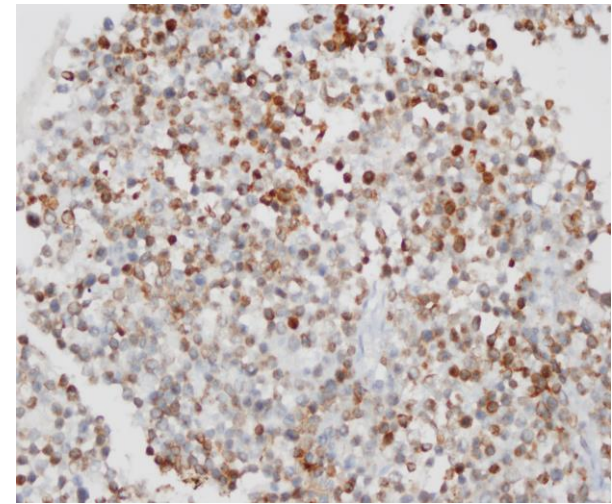
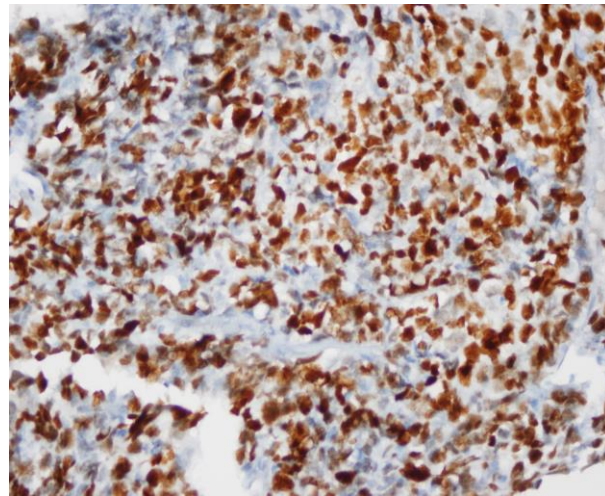
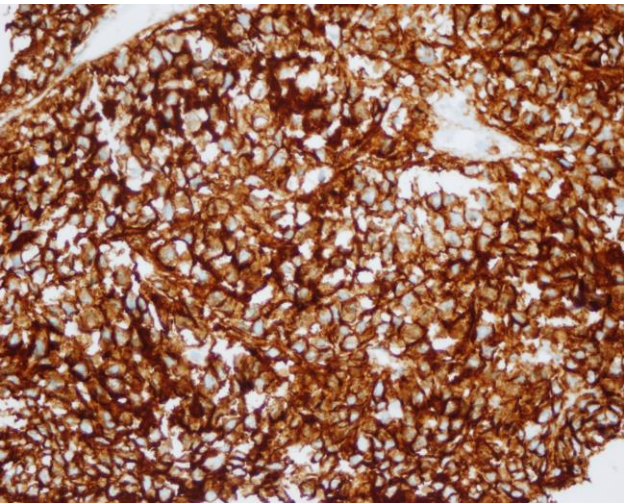
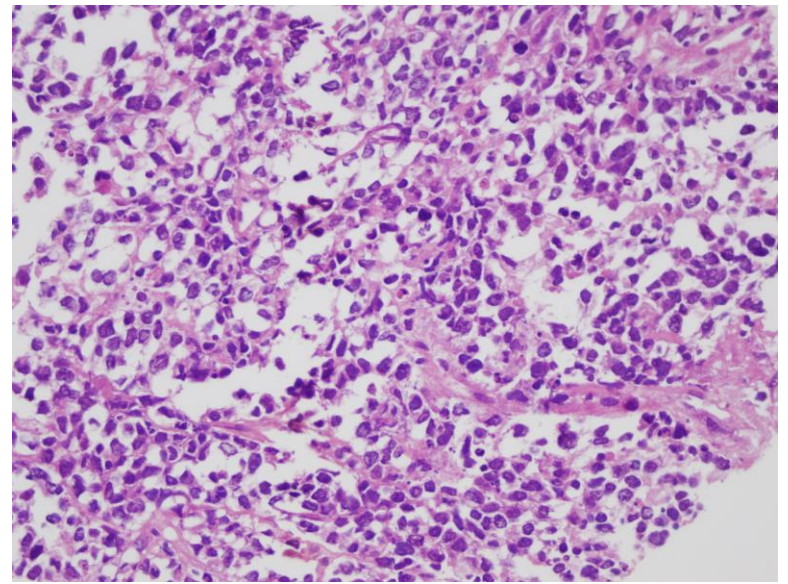
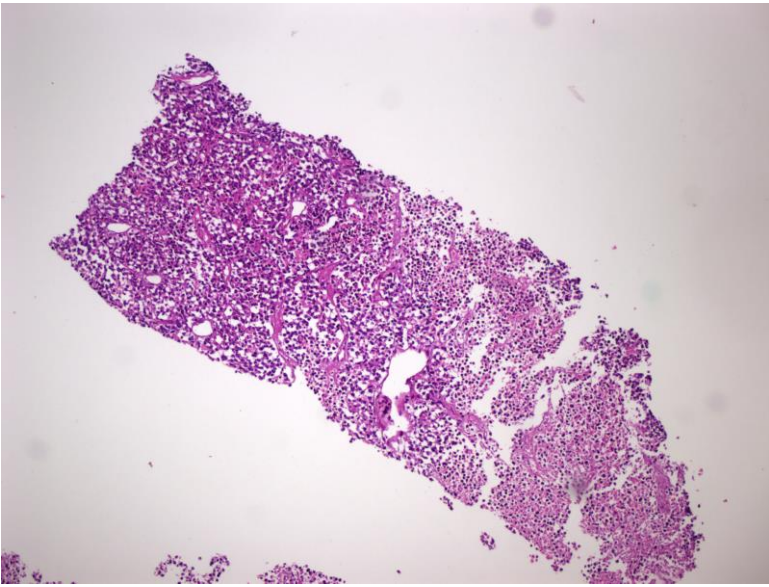
- FISH sonuçları
- 8q24 rearr.+
- t(8;14)(q24;q32)-
- 18q21 rearr. -
- t(14;18)(q32;q21)-
- 3q27 rearr-

Patolojik Tanı

- DBBHL,NOS. Germinal merkez benzeri (GCB-like) fenotip, myc ve bcl2 ekspresyonlu (double ekspresör)
- İmmunhistokimya sonuçları: c-myc+, bcl-2+
- FISH sonuçları:
 - 8q24 bölge rearr (+) ve t(8;14)(q24;q32)(-)
 - 18q21 bölge rearr (-) ve t(14;18)(q32;q21)(-)
 - 3q27 bölge rearr (-)

Vaka 5

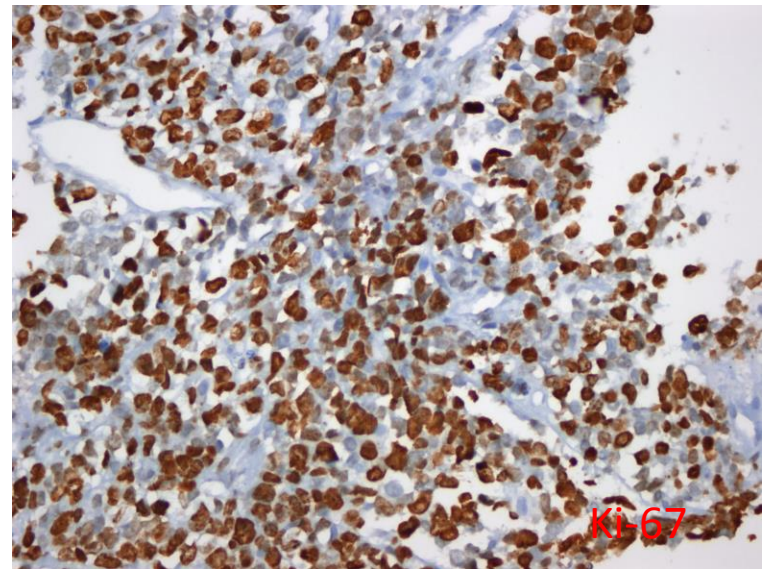
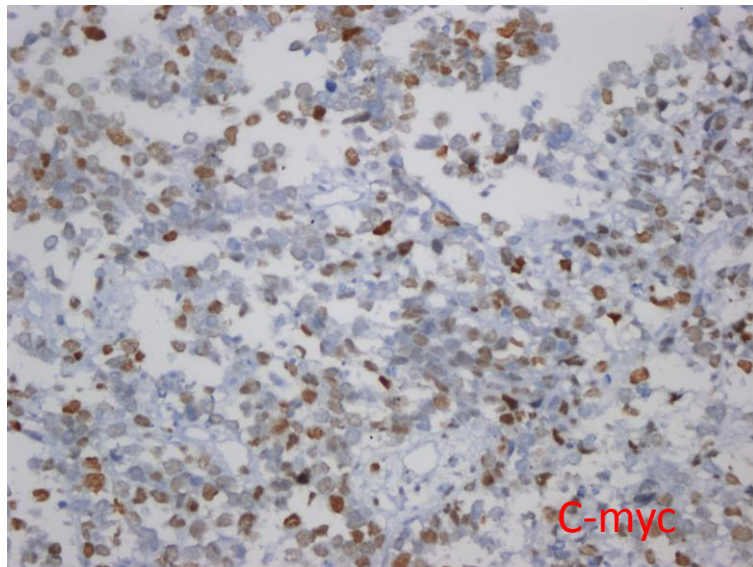
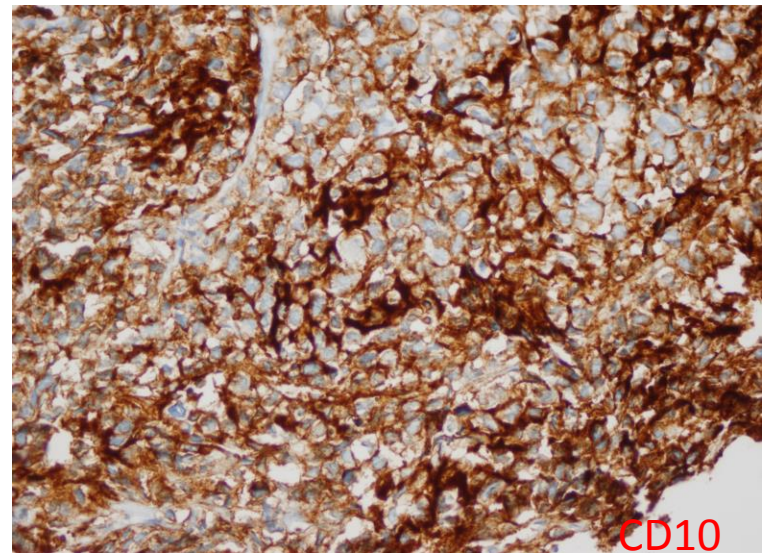
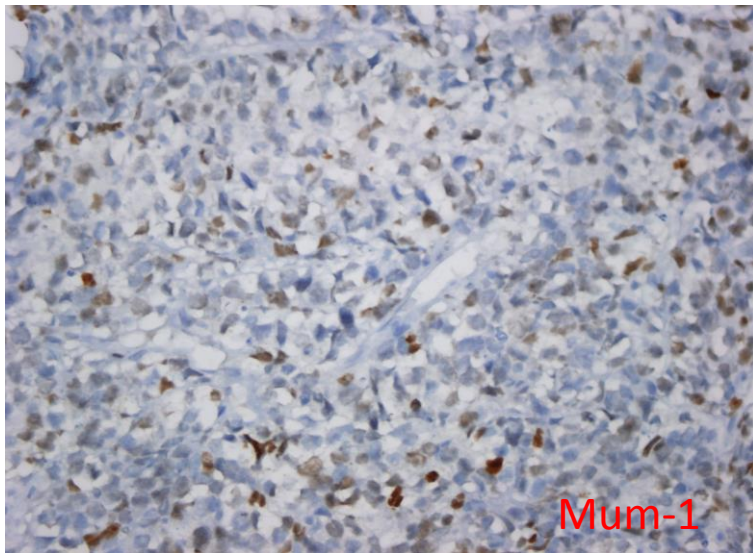
- 38y/K
- Karın ağrısı
- Batın USG'de multiple metastatik? Lezyonlar, paraaortik LAP+
- Krc bx.

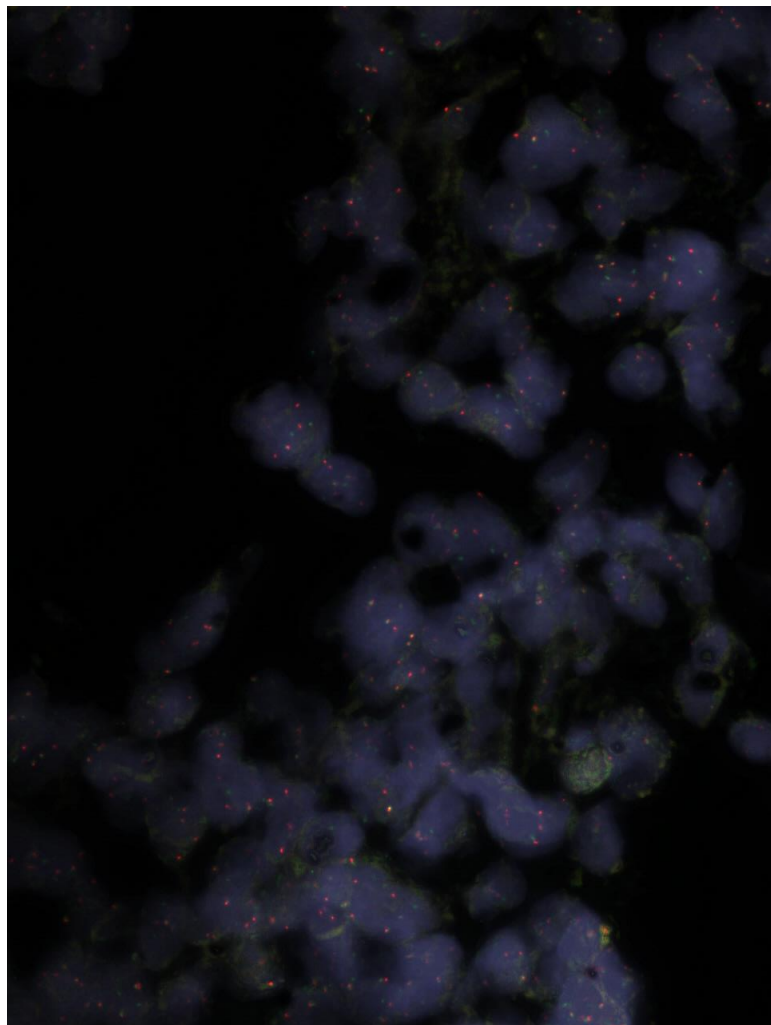


C
D
2

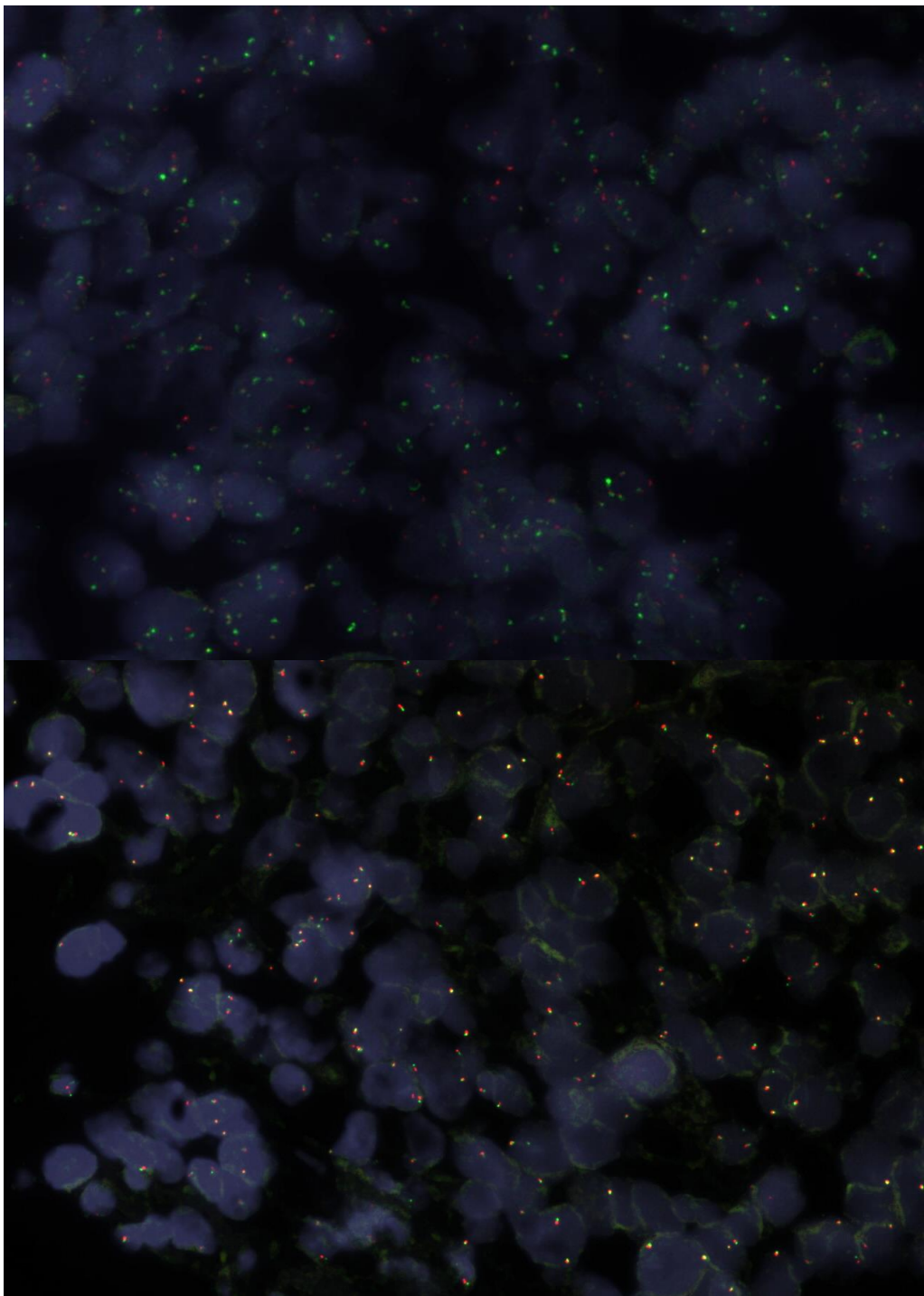
Bcl-6

Bcl-2





Bcl2 rearr+, t(14;18)+
8q24 rearr-, kopya < 4



- İHK sonuçları
- CD20+
- CD10+
- Bcl6+
- c-myc+
- Bcl-2+
- Ki-67 %80
- GCB

- FISH sonuçları
- 8q24 rearr.-
- t(8;14)(q24;q32) -
- 8q24 lokusda <4 kopya artışı
- 18q21 rearr. +
- t(14;18)(q32;q21)+
- 3q27 rearr.-

Patolojik Tanı

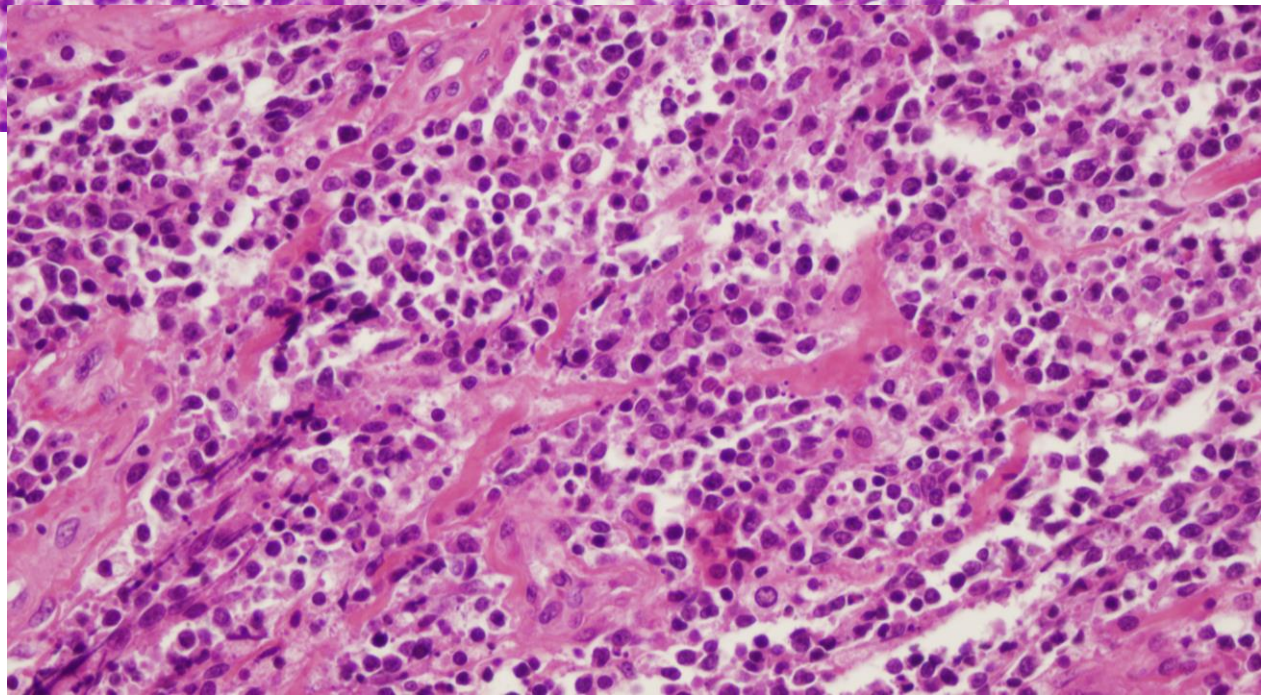
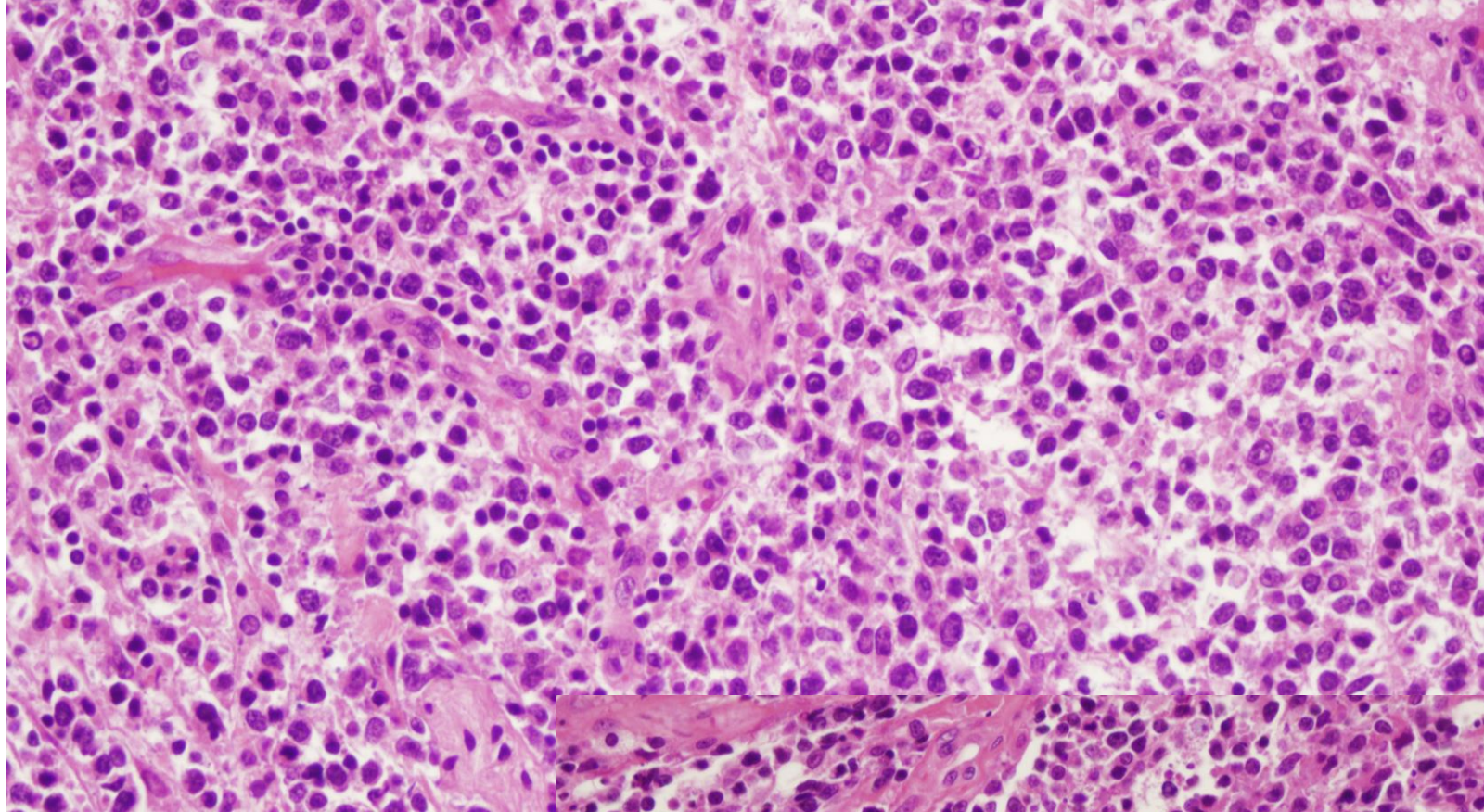
- DBBHL,NOS. Germinal merkez benzeri (GBC-like) fenotip, myc ve bcl2 ekspresyonlu (double ekspresör)
- İmmunhistokimya sonuçları: c-myc+, bcl-2+
- FISH sonuçları:
 - 8q24 rearr. ve t(8;14)(8q24;q32) -
 - 8q24<4 kopya
 - 18q21 rearr. ve t(14;18)(q32;q21)+

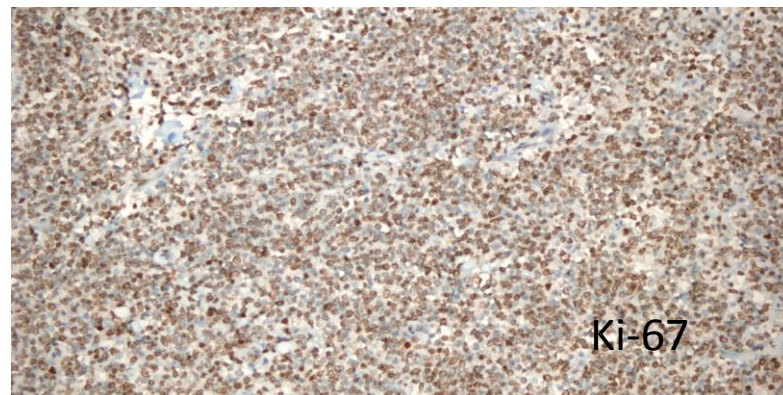
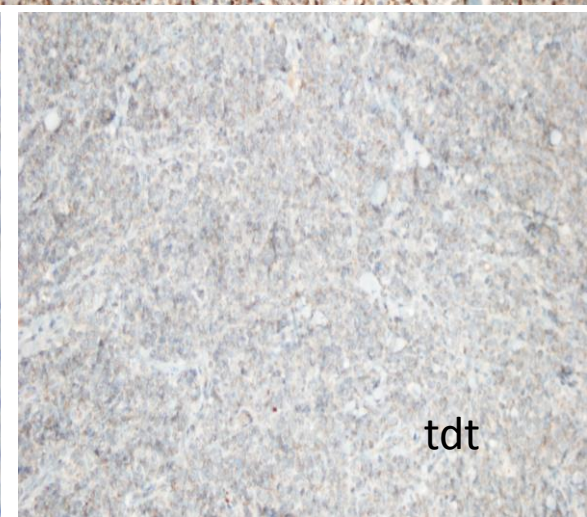
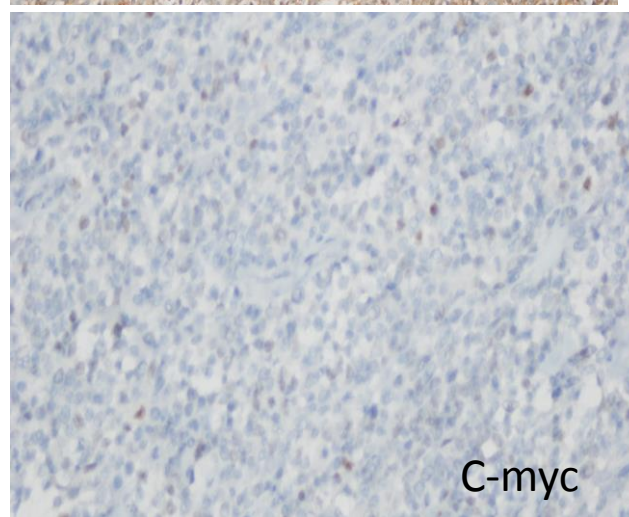
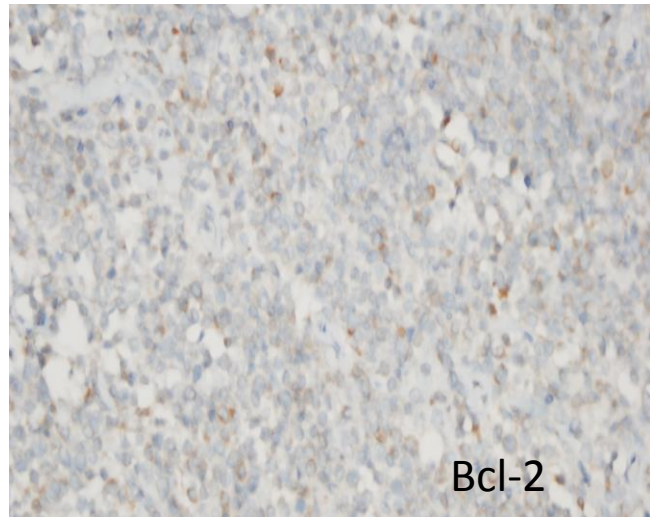
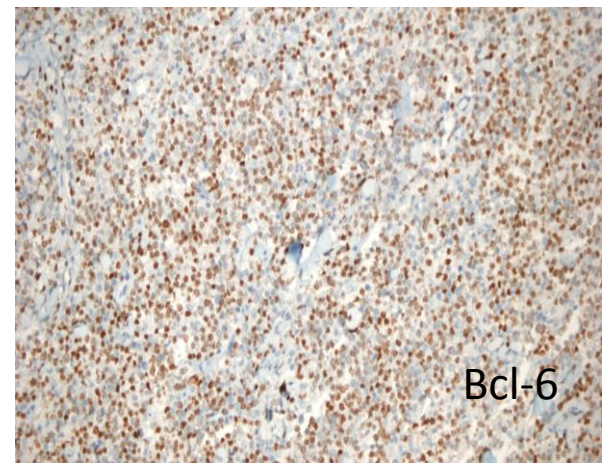
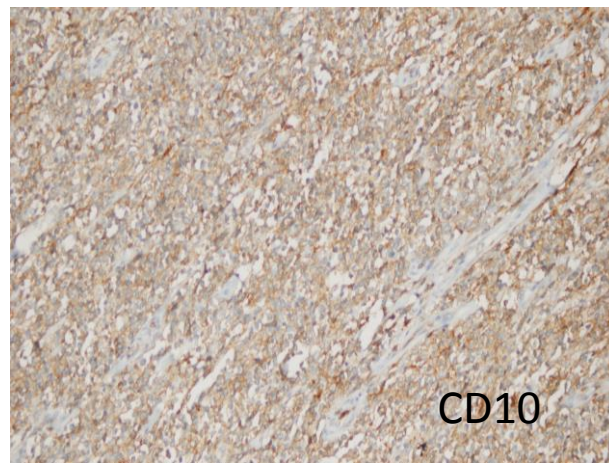
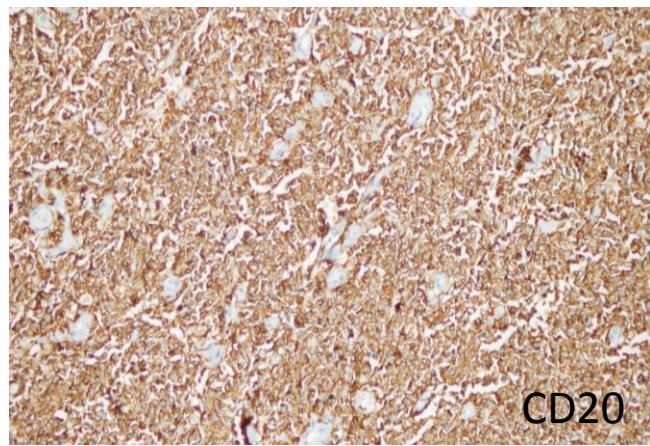
Yüksek gradeli B Hücreli lenfoma, NOS

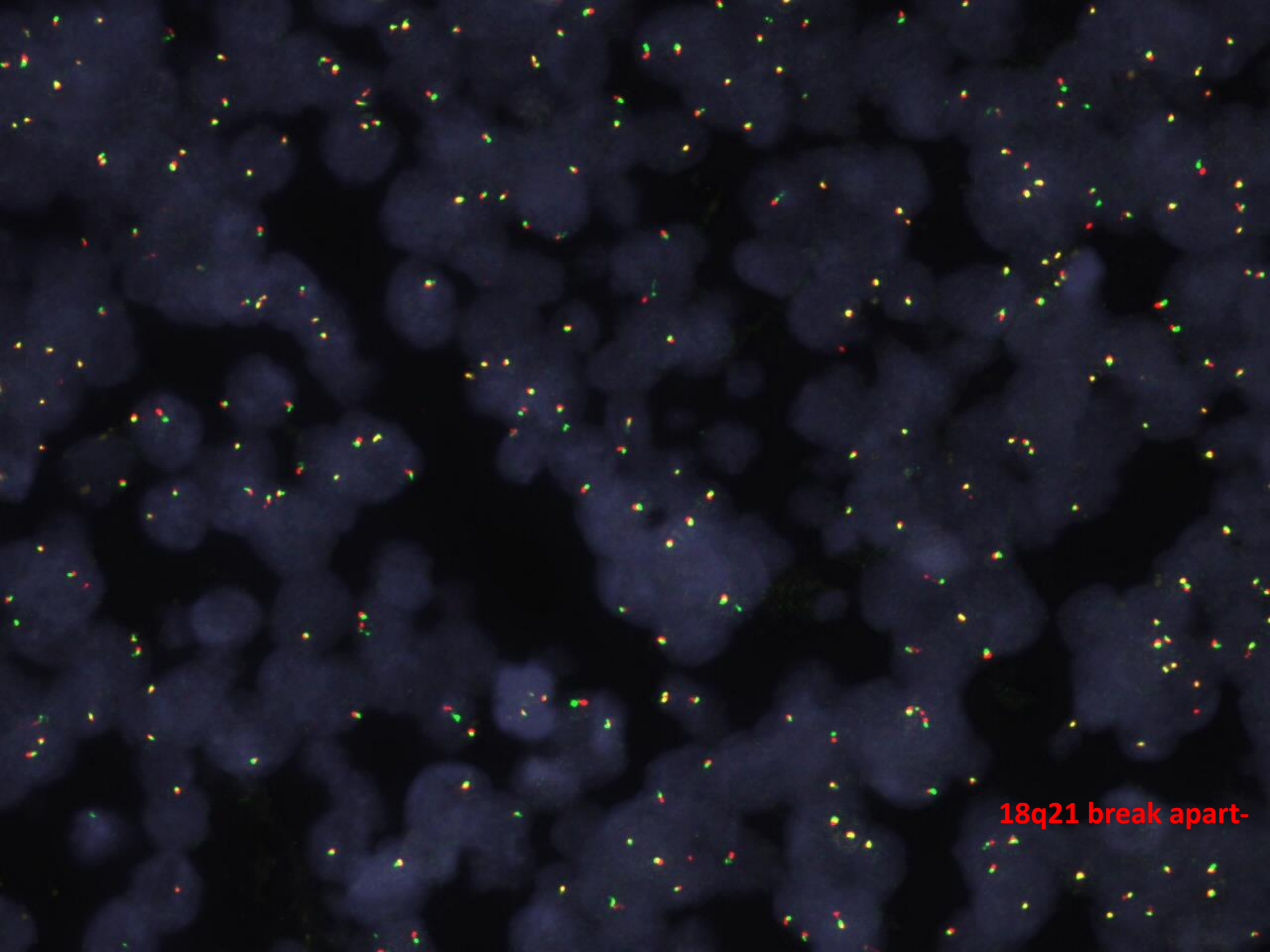
- DH ve triple hit olmayan unclassified DBBHL-BL ve blastoid morfolojili vakaları içermektedir
- Myc ve bcl-2 ve/veya bcl-6 rearrangementı (-)

Vaka 6

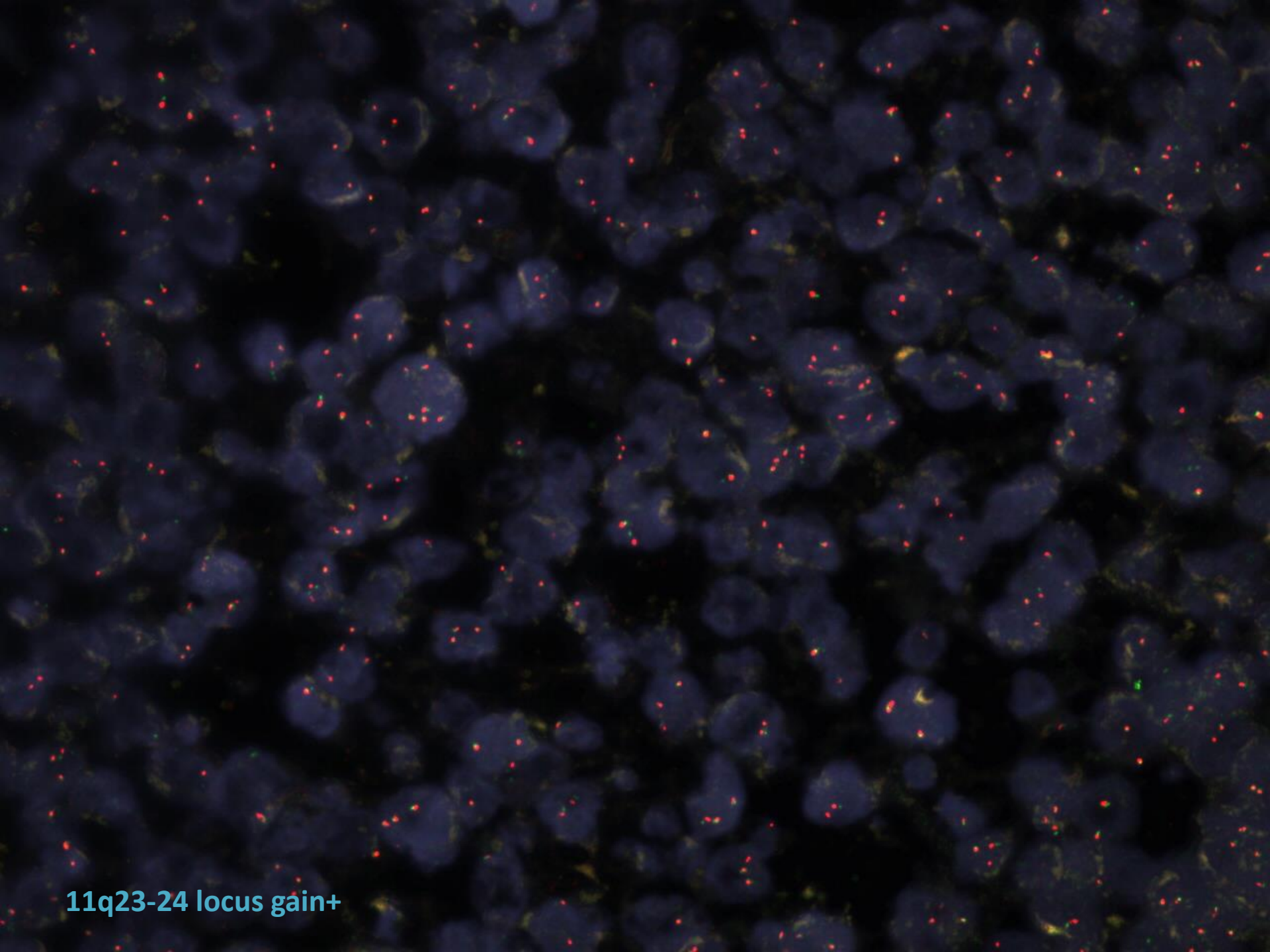
- 17y/E
- 1 aydır tekrarlayan karın ağrıları
- B semptomları-
- Batın sağ bölgede şişlik
- Hemogramda lökositozu+
- İnvaginasyon sebebi ile opere







18q21 break apart-



11q23-24 locus gain+

- İHK sonuçları
- **CD20+**
- **CD10+**
- **Bcl-6+**
- **C-myc -**
- Bcl-2-
- Mum-1-
- Ki-67 %95-100
- GCB

- FISH sonuçları
- 8q24 rearr.-
- t(8;14)(q24:32)-
- 18q21 rearr –
- 3q27 seyrek 3 kopya
- **KMT2A(11q23.3)+**
- **11q22.3 gain+**
- **11q23 gain+**

Patolojik tanı

- 11q aberasyonlu Burkitt-benzeri lenfoma.
- FISH sonuçları:
 - 8q24 bölge rearr. ve $t(8;14)(q24;q32)(-)$, 3q27 seyrek kopya(<4)
 - 11q22.3, 11q23 ve 11q23.3 bölgelerinde kazanım (gain)

11q aberasyonlu Burkitt-benzeri lenfoma

N Engl J Med. 2006 Jun 8;354(23):2419-30.

A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling.

Hummel M¹, Bentink S, Berger H, Klapper W, Wessendorf S, Barth TF, Bernd HW, Cogliatti SB, Dierlamm J, Feller AC, Hansmann ML, Haralambieva E, Harder L, Hasenclever D, Kühn M, Lenze D, Lichter P, Martin-Subero JI, Möller P, Müller-Hermelink HK, Ott G, Parwaresch RM, Pott C, Rosenwald A, Rosolowski M, Schwaenen C, Stürzenhofecker B, Szczepanowski M, Trautmann H, Wacker HH, Spang R, Loeffler M, Trümper L, Stein H, Siebert R; Molecular Mechanisms in Malignant Lymphomas Network Project of the Deutsche Krebshilfe.

Author information

Abstract

BACKGROUND: The distinction between Burkitt's lymphoma and diffuse large-B-cell lymphoma is unclear. We used transcriptional and genomic profiling to define Burkitt's lymphoma more precisely and to distinguish subgroups in other types of mature aggressive B-cell lymphomas.

METHODS: We performed gene-expression profiling using Affymetrix U133A GeneChips with RNA from 220 mature aggressive B-cell lymphomas, including a core group of 8 Burkitt's lymphomas that met all World Health Organization (WHO) criteria. A molecular signature for Burkitt's lymphoma was generated, and chromosomal abnormalities were detected with interphase fluorescence in situ hybridization and array-based comparative genomic hybridization.

RESULTS: We used the molecular signature for Burkitt's lymphoma to identify 44 cases: 11 had the morphologic features of diffuse large-B-cell lymphomas, 4 were unclassifiable mature aggressive B-cell lymphomas, and 29 had a classic or atypical Burkitt's morphologic appearance. Also, five did not have a detectable IG-myc Burkitt's translocation, whereas the others contained an IG-myc fusion, mostly in simple karyotypes. Of the 176 lymphomas without the molecular signature for Burkitt's lymphoma, 155 were diffuse large-B-cell lymphomas. Of these 155 cases, 21 percent had a chromosomal breakpoint at the myc locus associated with complex chromosomal changes and an unfavorable clinical course.

CONCLUSIONS: Our molecular definition of Burkitt's lymphoma clarifies and extends the spectrum of the WHO criteria for Burkitt's lymphoma. In mature aggressive B-cell lymphomas without a gene signature for Burkitt's lymphoma, chromosomal breakpoints at the myc locus were associated with an adverse clinical outcome.

Journal of Pathology

J Pathol 2008; 216: 440–450

Published online 14 July 2008 in Wiley InterScience

(www.interscience.wiley.com) DOI: 10.1002/path.2410

Original Paper

MYC translocation-negative classical Burkitt lymphoma cases: an alternative pathogenetic mechanism involving miRNA deregulation

E Leucci,¹ M Cocco,¹ A Onnis,¹ G De Falco,¹ P van Cleef,² C Bellan,¹ A van Rijk,² J Nyagol,¹ B Byakika,³ S Lazzi,¹ P Tosi,¹ H van Krieken² and L Leoncini¹*

¹Department of Human Pathology and Oncology, University of Siena, Italy

²Department of Pathology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

³The Nairobi Hospital, Nairobi, Kenya

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L Leoncini, MD Department of Human Pathology and Oncology, University of Siena, Via delle Scotte, 6 - 53100 - Siena, Italy.
E-mail: leoncinil@unisi.it

No conflicts of interest were

Abstract

The molecular feature of Burkitt lymphoma (BL) is the translocation that places c-Myc under the control of immunoglobulin gene regulatory elements. However, there is accumulating evidence that some cases may lack an identifiable MYC translocation. In addition, during the EUROFISH project, aiming at the standardization of FISH procedures in lymphoma diagnosis, we found that five cases out of 35 classic endemic BLs were

11q aberasyonlu Burkitt-benzeri lenfoma

- Fenotipik ve GEP, BL gibi fakat myc rearr.(-)
- Kromozom 11q deęişiklikleri; prox. gain ya da telomerik kayıplarla ilişkili
(11q12-q13/ q23-24 gain veya amplifikasyonu
11q23/24-qter kaybı)
- Kompleks karyotip, düşük myc ekspresyonu, sitolojik pleomorfizm
- Sıklıkla nodal prezentasyon
- Pediatrik BL %10
- Klinik seyri BL gibi

Epstein-Barr virus pozitif (EBV+) DBBHL NOS WHO 2008 “EBV+ DLBCL of the elderly”

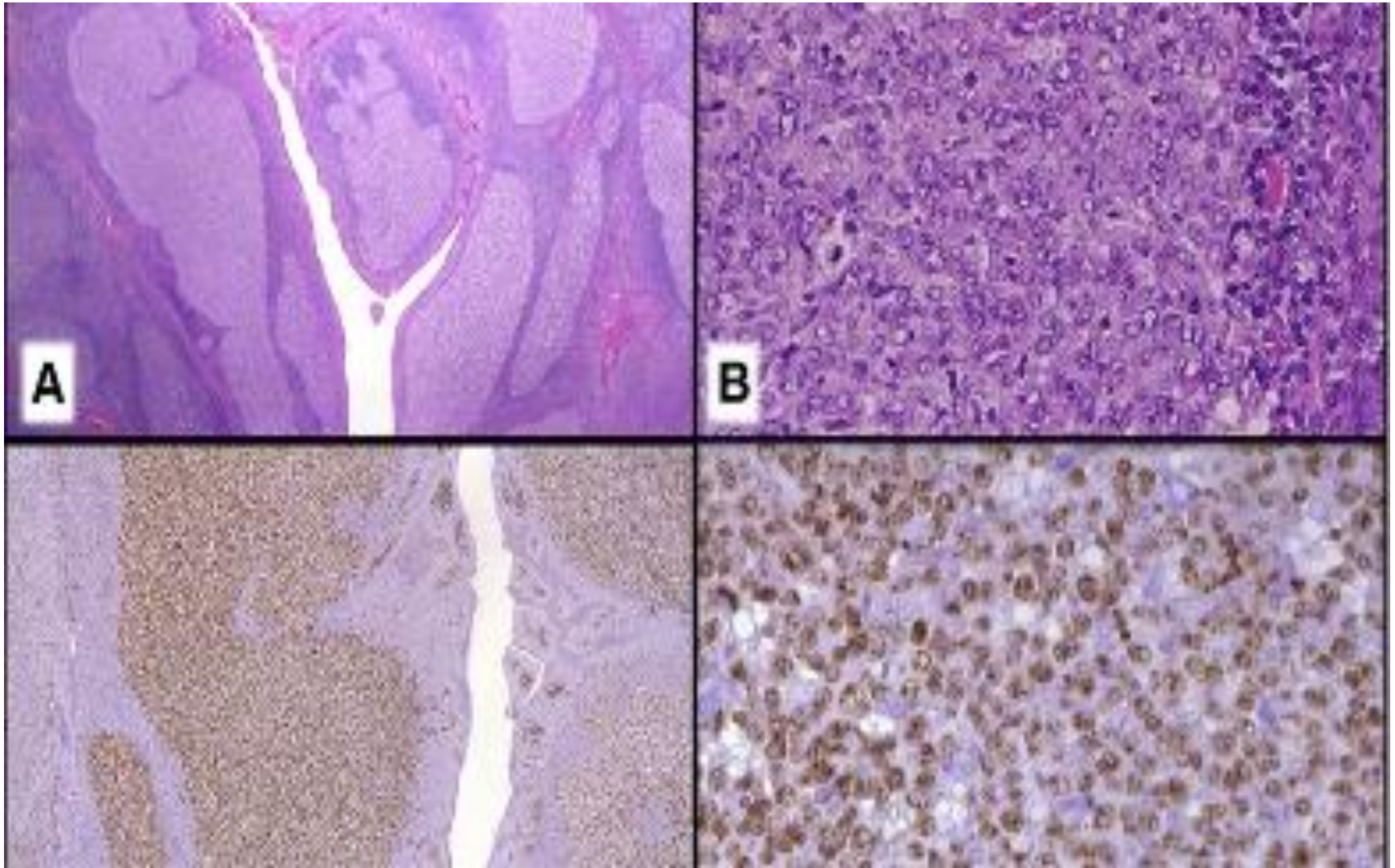
- >50y
- EBV(-) vakalara göre daha kötü prognozlu
- Gençlerde de olabilir, survisi daha iyi

EBV+ mukokutenöz ülser (provisional entity)

- Kendini sınırlayan büyüme paternine sahip
- Konservatif tedaviye yanıtı
- İleri yaş ve immünyetmezlikli hastalar

IRF4 rearrangementli DBBHL

- Waldeyer halkası ve/veya servikal lenf düğümleri, erken evre
- Foliküler, foliküler ve difuz veya FL grade 3b benzeyen pür difuz pattern veya DBBHL
- Bcl-6 ile kuvvetli *IRF4/MUM1* ekspresyonu ve yüksek proliferasyon indeksi
- CD10 ve bcl2, ½ vakada eksprese; bcl2 rearr(-)
- GEP → Germinal merkez tip
- Pediatrik tip FL'den daha agresif
- KT'ye iyi yanıt

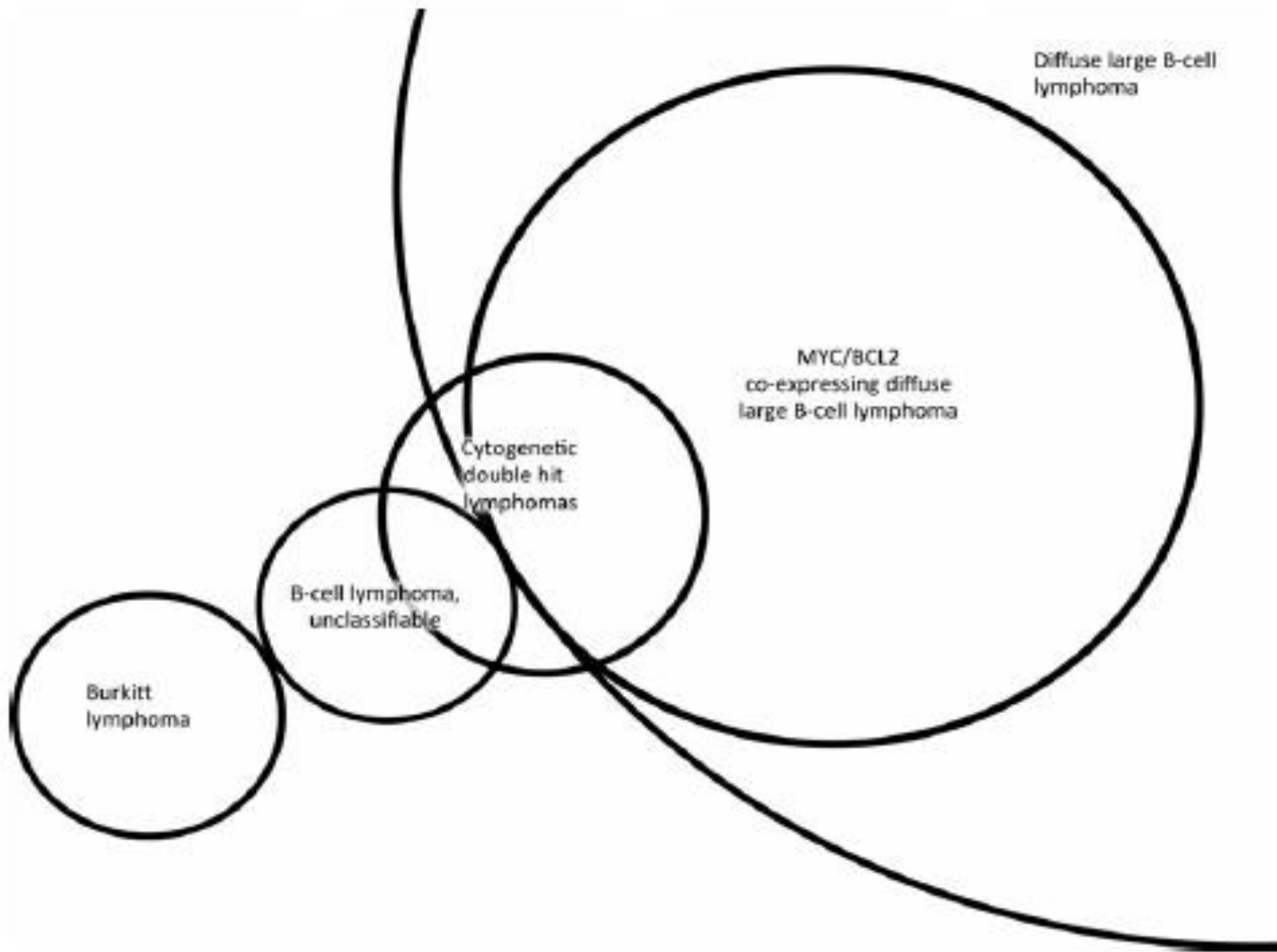


Bcl-6

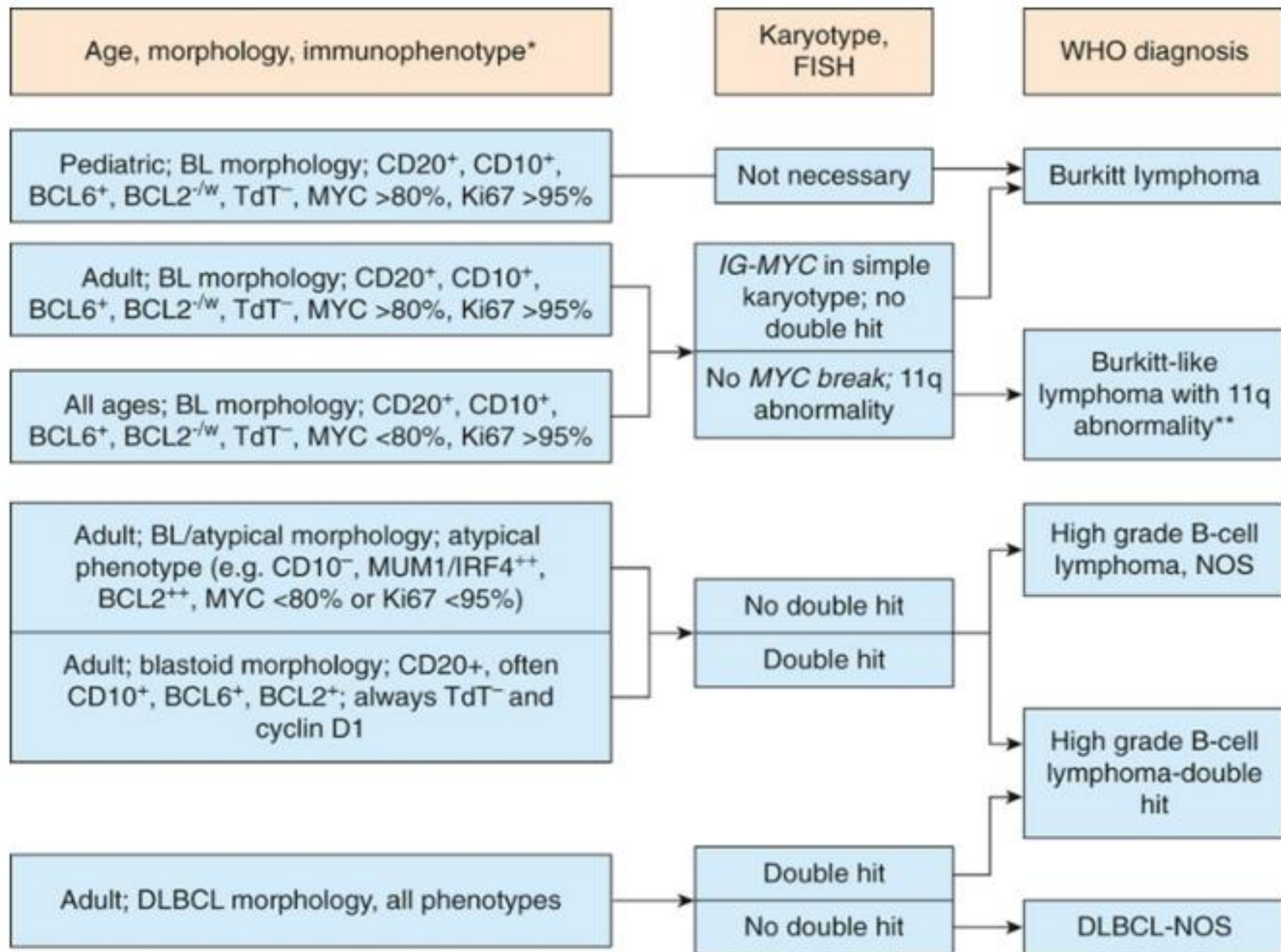
MUM1

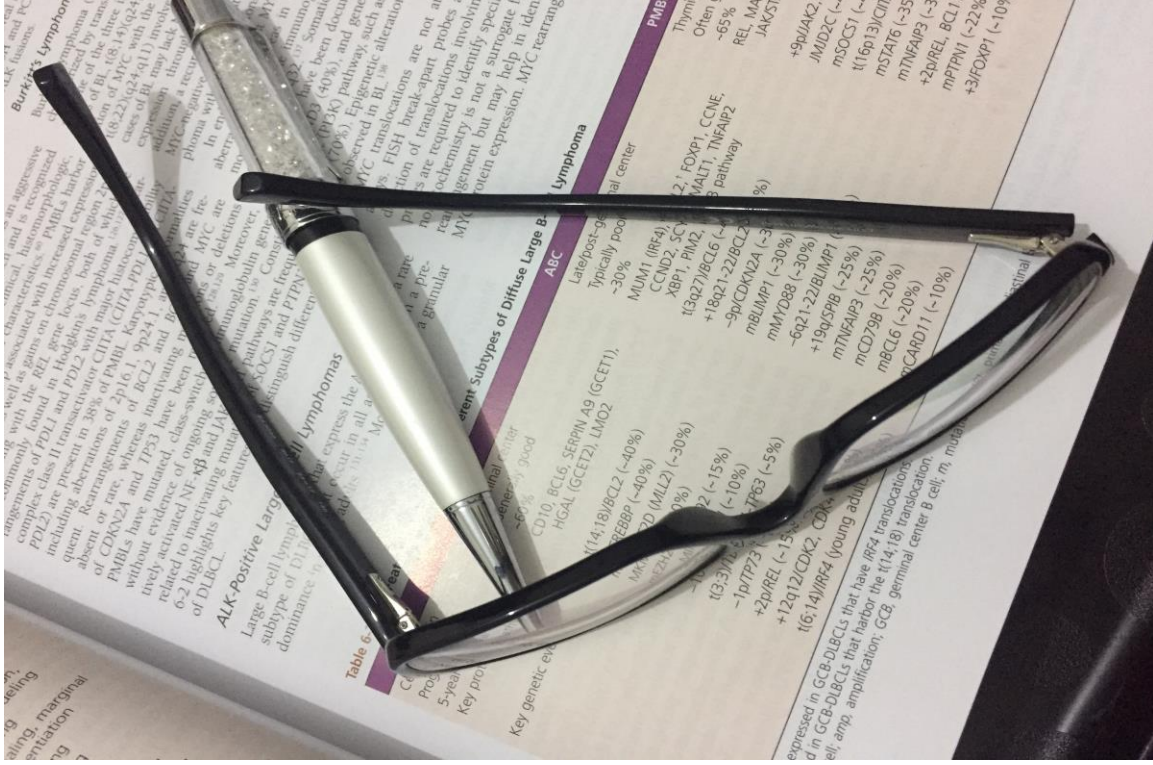
The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Steven H. Swerdlow, et al. Blood 2016 127:2375-2390

Özetle



Cheah CY ve ark. *Brit J Haemat* 2014; doi: 10.1111/bjh.13276





Teşekkür ederim...