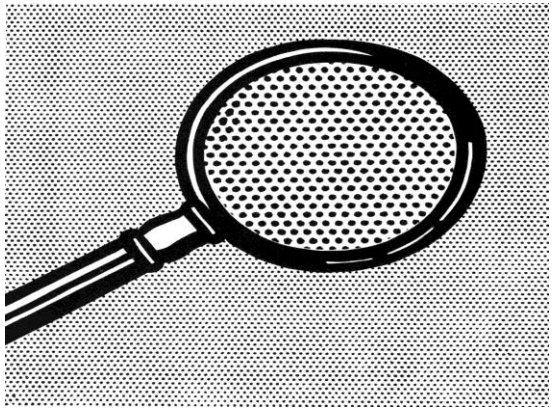
DGHO online - 12. Mai 2023

onkopedia

Neue WHO Klassifikation: Lymphatische Neoplasien

Übersicht Pathologie



Roy Lichtenstein

Prof. Dr. Ilske Oschlies

Institut für Pathologie

Sektion Hämatopathologie/Lymphknotenregister

Universitätsklinikum Schleswig-Holstein- Campus Kiel

Offenlegung Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition
2. Beratungs- bzw. Gutachtertätigkeit
3. Besitz von Geschäftsanteilen, Aktien oder Fonds
4. Patent, Urheberrecht, Verkaufslizenz
5. Honorare
6. Finanzierung wissenschaftlicher Untersuchungen
7. Andere finanzielle Beziehungen
8. Immaterielle Interessenkonflikte

Ich sehe keine Interessenskonflikte

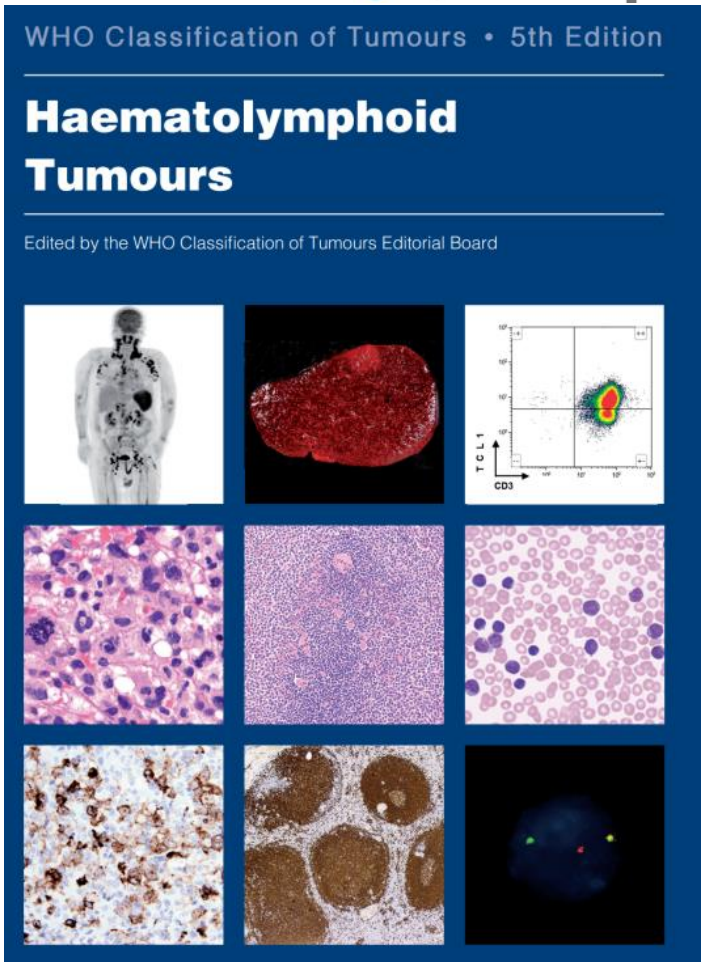
WHO 2000„blue book“
350 Seiten 3rd edition

↓ **WHO 2008**
4th edition

WHO 2016/2017
revised 4th edition
585 Seiten

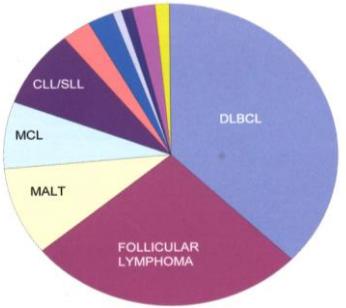
↓

WHO 2023 5th edition
Print ?? Seiten (und online!)



Fokus auf die häufigsten Entitäten

Was ist neu/anders in der WHOHAEM5?



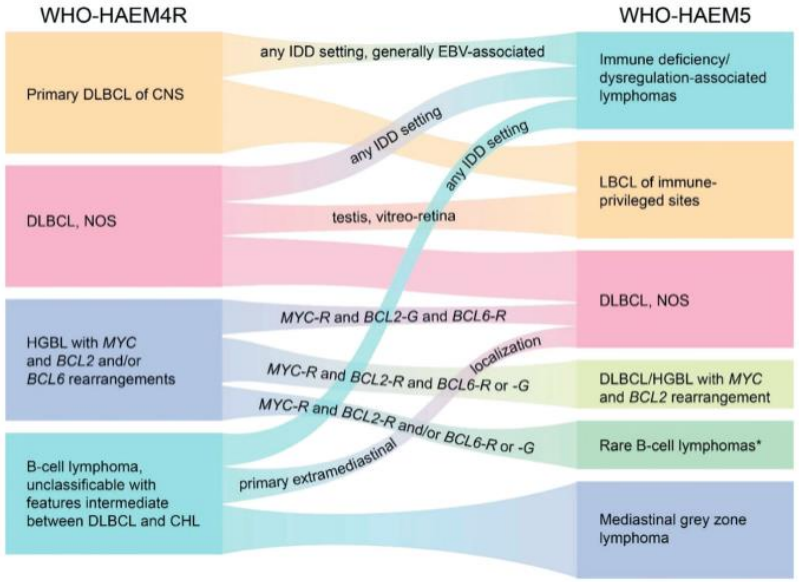
- Großzellige B-Zell-Lymphome
- Follikuläre Lymphome
- Lymphoproliferationen und Lymphome assoziiert mit Immundefizienz und Immundysregulation

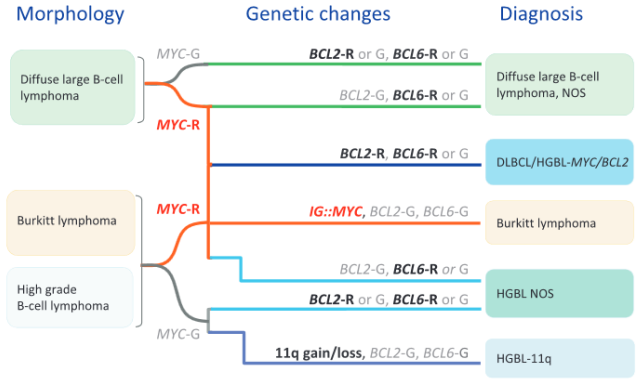
Fokus auf die häufigsten Entitäten

Was ist neu/anders in der WHOHAEM5?

- Großzellige B-Zell-Lymphome
- Follikuläre Lymphome
- Lymphoproliferationen und Lymphome assoziiert mit Immundefizienz und Immundysregulation

„Bewegung“ bei den aggressiven B-NHLs






www.nature.com/leu Leukemia

REVIEW ARTICLE OPEN

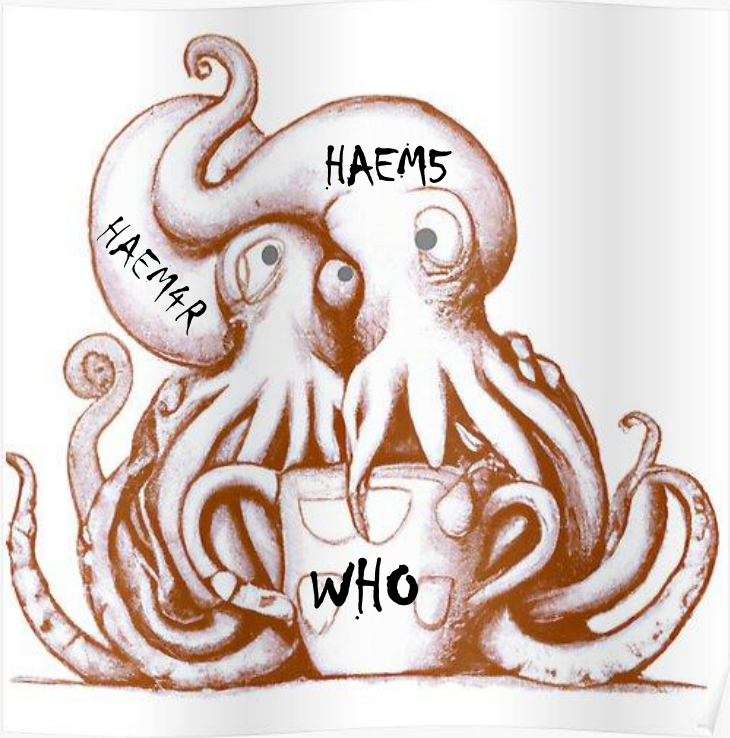
LYMPHOMA

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

Rita Alaggio[1], Catalina Amador[2], Ioannis Anagnostopoulos[3], Ayoma D. Attygalle[4], Iguaracyra Barreto de Oliveira Araujo[5], Emilio Berti[6], Govind Bhagat[7], Anita Maria Borges[8], Daniel Boyer[9], Mariarita Calaminici[10], Amy Chadburn[11], John K. C. Chan[12], Wah Cheuk[13], Wee-Joo Chng[13], John K. Choi[14], Shih-Sung Chuang[15], Sarah E. Coupland[16], Magdalena Czader[17], Sandeep S. Dave[18], Daphne de Jong[19], Ming-Qing Du[20,21], Kojo S. Elenitoba-Johnson[22], Judith Ferry[23,24], Julia Geyer[25], Dita Gratzinger[26], Joan Guitart[27], Sumeet Gujral[28], Marian Harris[29], Christine J. Harrison[30], Sylvia Hartmann[31], Andreas Hochhaus[32], Patty M. Jansen[33], Kennosuke Karube[34], Werner Kempf[35], Joseph Khoury[36], Hiroshi Kimura[37], Wolfram Klapper[38], Alexandra E. Kovach[39], Shaji Kumar[40], Alexander J. Lazar[41], Stefano Lazzi[42], Lorenzo Leoncini[43], Nelson Leung[44], Vasiliki Leventaki[45], Xiao-Qiu Li[46], Megan S. Lim[47], Wei-Ping Liu[48], Abner Louissaint Jr.[49], Andrea Marcogliese[50], L. Jeffrey Medeiros[51], Michael Michal[52], Roberto N. Miranda[53], Christina Mitteldorf[54], Santiago Montes-Moreno[55], William Morice[56], Valentina Nardi[57], Kikkeri N. Naresh[58], Yasodha Natkunam[59], Siok-Bian Ng[60], Ilske Oschlies[61], German Ott[62,63], Marie Parrens[64], Melissa Pullitzer[65], S. Vincent Rajkumar[66], Andrew C. Rawstron[67], Karen Rech[68], Andreas Rosenwald[69], Jonathan Said[70], Clementine Sarkozy[71], Shahin Sayed[72], Caner Saygin[73], Anna Schuh[74], William Sewell[75], Reiner Siebert[76,77], Aliyah R. Sohani[78], Reuben Tooze[79], Alexandra Traverse-Glehen[80], Francisco Vega[81], Beatrice Vergier[82], Ashutosh D. Wechalekar[83], Brent Wood[84], Luc Xerri[85] and Wenbin Xiao[53]

Alaggio R. et al. Leukemia 2022

…und doch vieles unverändert…



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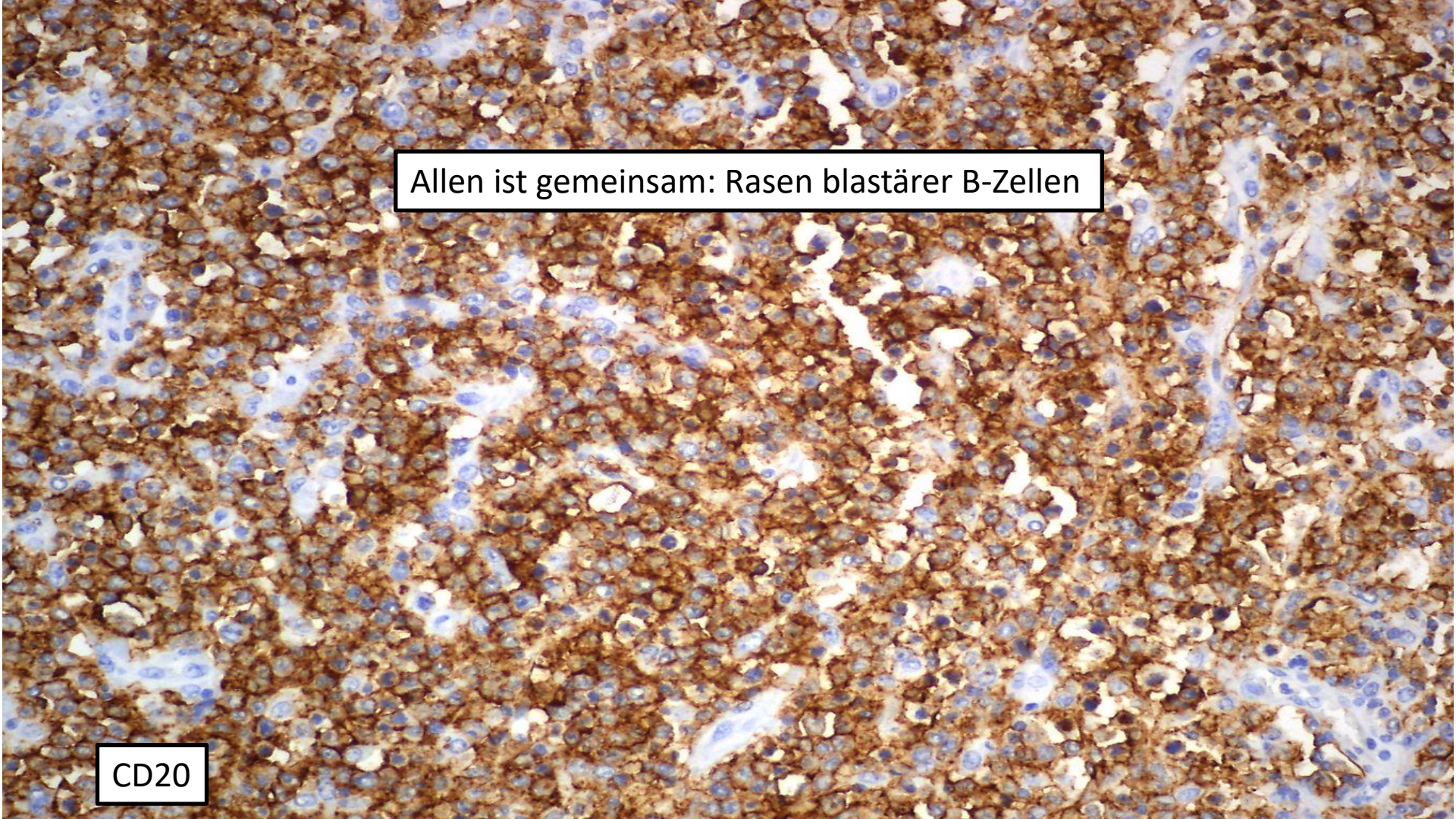
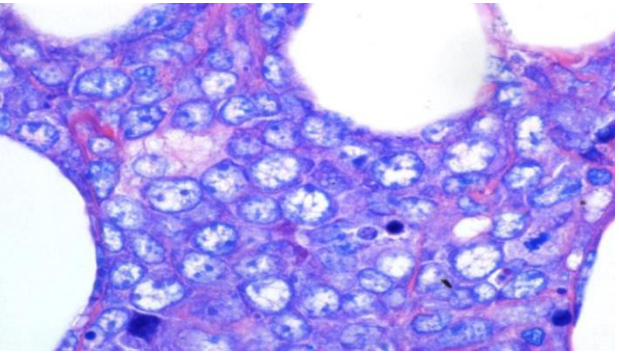
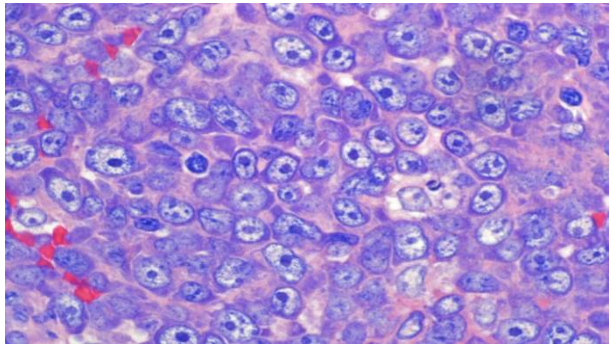
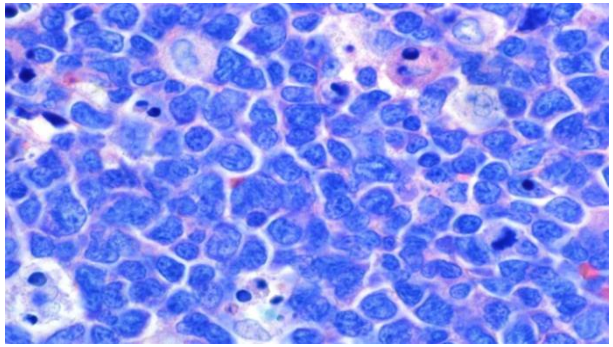
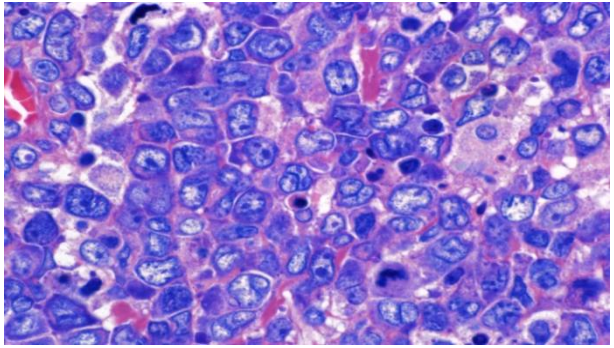
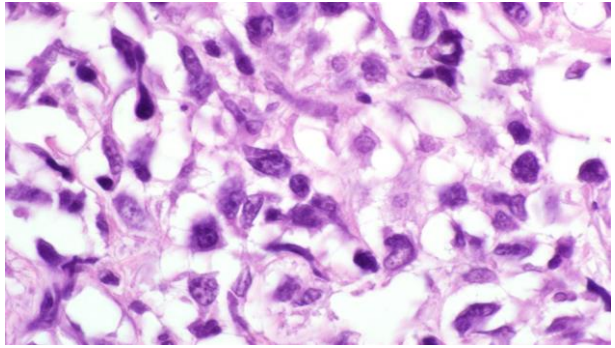
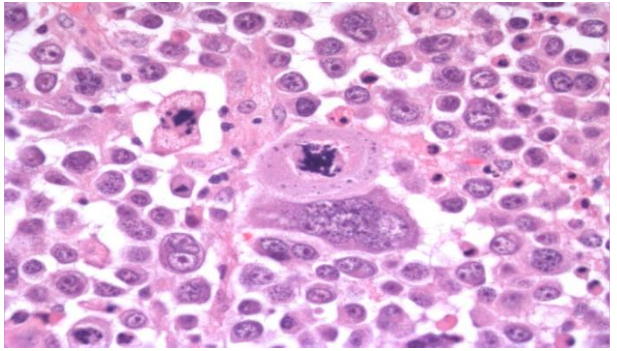
Großzellige B-Zell-Lymphome

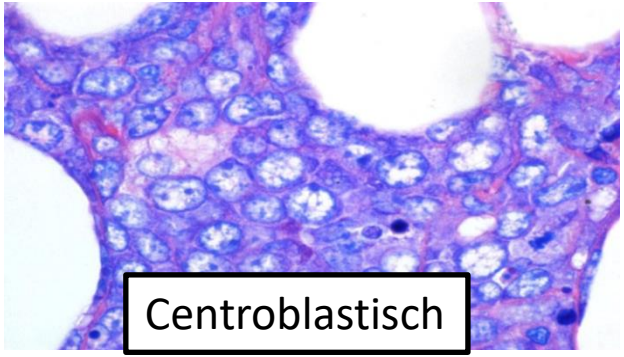
Was sieht der Pathologe?

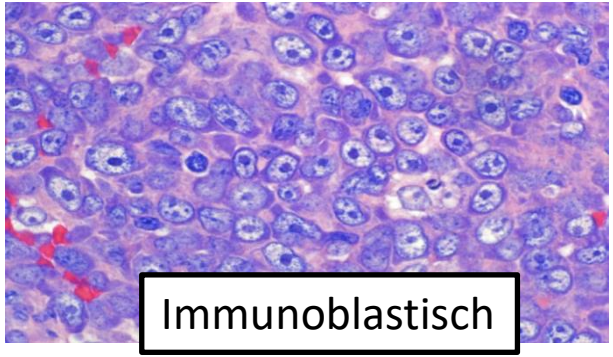
- Rasen blastärer Zellen (selten paucizellulär)
- Blast definiert über die Zellgröße und Kernchromatin
- B-Zell-Phänotyp, meist CD20+

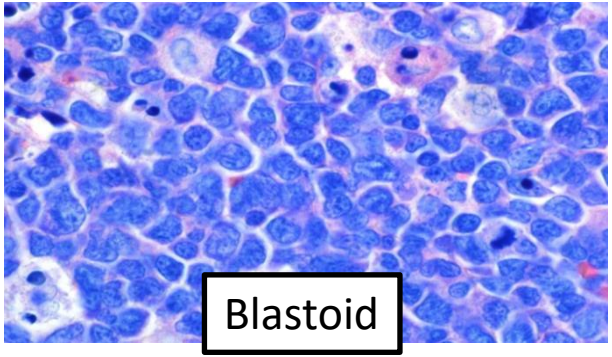

Allen ist gemeinsam: Rasen blastärer B-Zellen
CD20

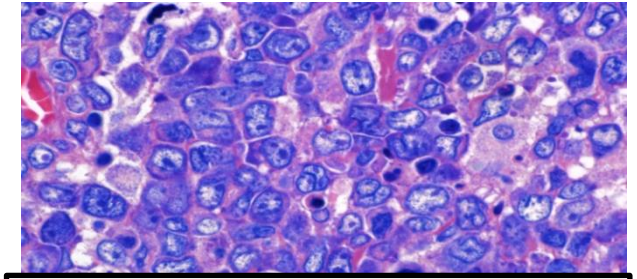







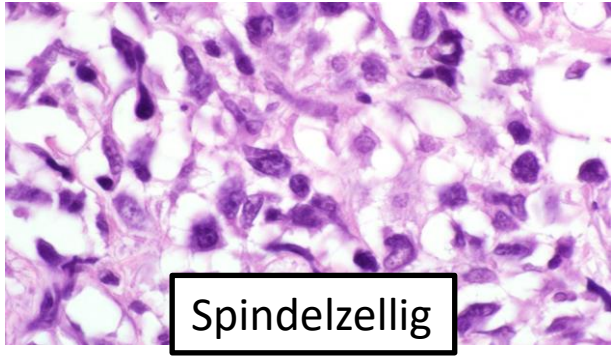
zytologische Vielfalt „großzelliger/blastärer B-Zell-Lymphome“

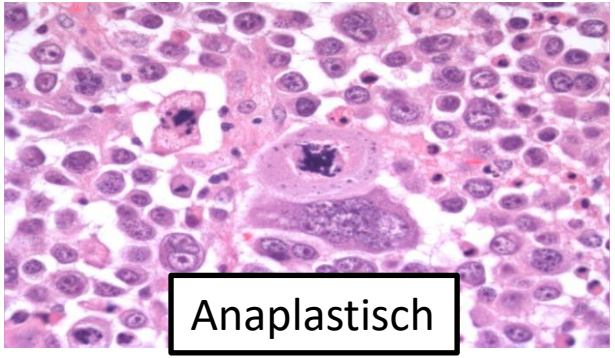

Centroblastisch


Immunoblastisch


Blastoid

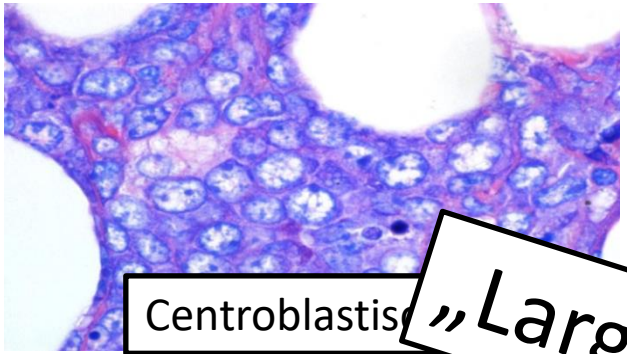

Centroblastisch multilobuliert


Spindelzellig

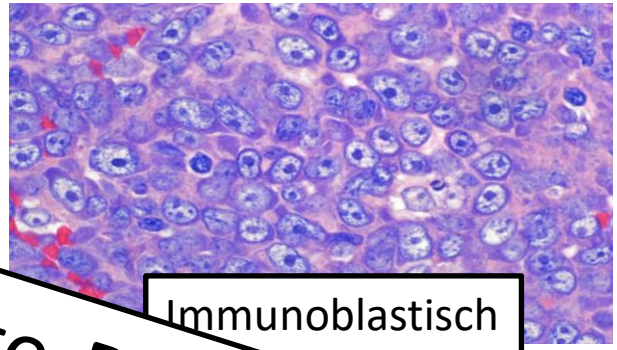

Anaplastisch

Zytologische „Subtypisierung“- Basis für weitere Immunphänotypisierung

zytologische Vielfalt „großzelliger/blastärer B-Zell-Lymphome“



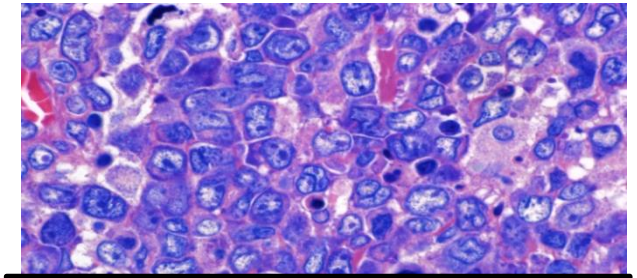
Centroblastisch



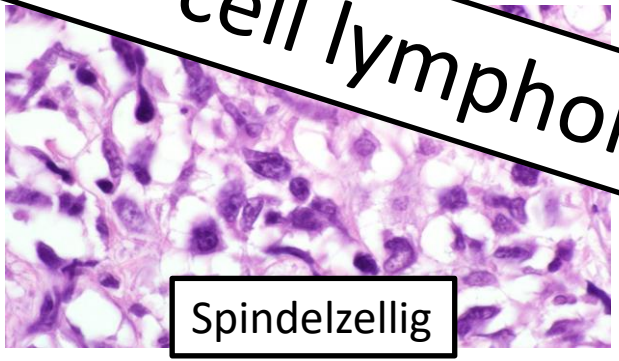
Immunoblastisch

„High grade“-“blastoid“-“dark-zone“

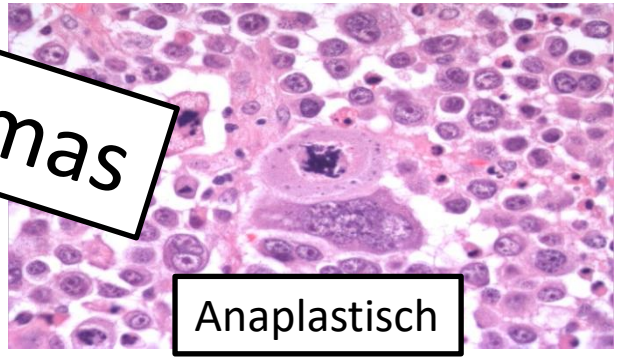
„Large-B“ cell lymphomas



Centroblastisch multilobuliert



Spindelzellig



Anaplastisch

Zytologische „Subtypisierung“- Basis für weitere Immunphänotypisierung/molekulare Diagnostik zur Klassifikation

WHOHAEM5-Large B-cell lymphomas

Transformations of indolent B-cell lymphomas
Transformations of indolent B-cell lymphomas
Large B-cell lymphomas
Diffuse large B-cell lymphoma, NOS
T-cell/histiocyte-rich large B-cell lymphoma
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
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Mediastinal grey zone lymphoma
High-grade B-cell lymphoma, NOS

Mature B-cell lymphoma (Kategorie)

Large B-cell lymphoma (Familie/Klasse)

Entität (z.B. DLBCL,NOS)

Subtyp (GCB-like DLBCL, NOS)

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Mediastinal grey zone lymphoma
High-grade B-cell lymphoma, NOS
Burkitt lymphoma
Burkitt lymphoma
KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas
Primary effusion lymphoma
KSHV/HHV8-positive diffuse large B-cell lymphoma

Transformierte Lymphome separiert in andere Klasse

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Transformierte Lymphome separiert in andere Klasse

klinisch Verdacht bei bekanntem indolenten NHL

- LDH > 2x obere Norm
- Hyperkalziämie
- Neue/rapid zunehmende Zytopenie
- diskonkordante Lymphadenopathie/extranodal

Biopsie aus **PET+** (SUV>5) Läsion

Pathologie: Transformation in klonal verwandtes aggressives Lymphom

WHOHAEM5-Large B-cell lymphomas

17 spezifische Entitäten

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Morphologie

Molekular definiert

Virus-associated

Lokalisation

Other

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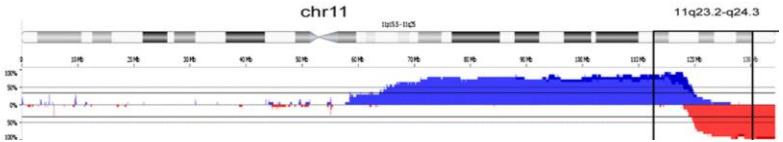
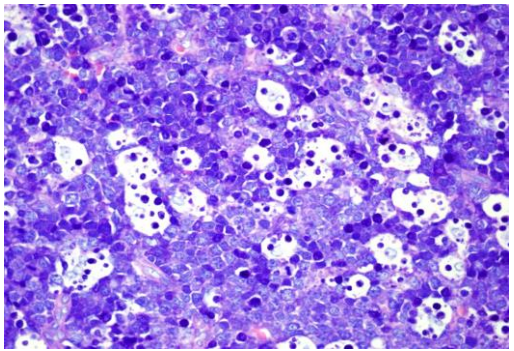
neuer Name für seltene molekular definierte Entität

High grade/(ICC: großzelliges) B-Zell Lymphom mit 11q Alteration - früher„Burkitt-artiges Lymphom“

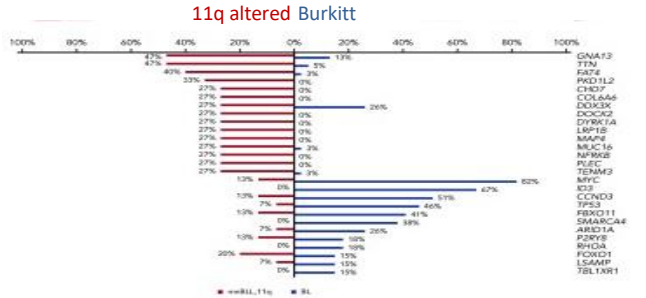
- Lymphome, die histopathologisch, klinisch und in ihrer Genexpression dem Burkitt Lymphom sehr ähnlich sind. Aber: kein *MYC* Bruch.

- Rekurrente Alterationen von *11q*.





- *Mutationsprofil ist anders als beim Burkitt Lymphom.*



Salaverria I. et al, Blood 2014; Ferreiro JF et al, Haematol 2015; Wagener R. 2019; Gonzales-Farre B. et al, Haematologica 2019 Au Xeung 2020

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„fluid-overload -associated lymphoma“
- eine neue extrem seltene Entität

WHOHAEM5-Large B-cell lymphomas: Neue Entität des „fluid overload“ assoziierten Lymphoms

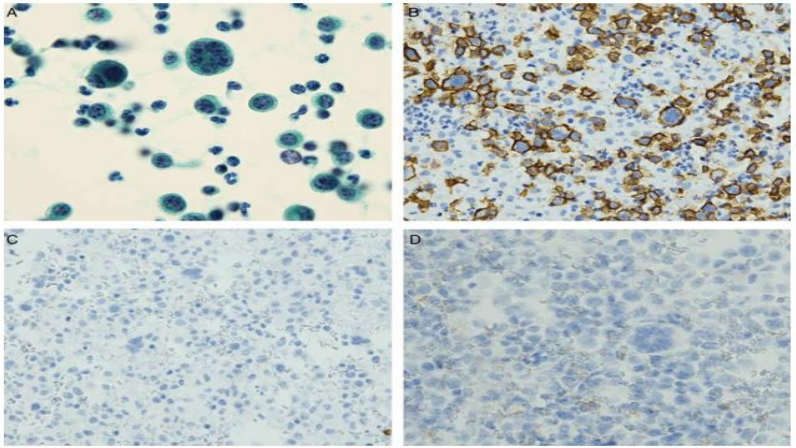

FIGURE 1. Pleural effusion in case 66 reveals large, pleomorphic atypical lymphoid cells with conspicuous nucleoli and small to moderate amounts of cytoplasm. A, Some cells have multiple nuclei (Papanicolaou stain). Immunohistochemical analysis reveals that the cells are positive forCD138 (B), and negative for CD20 (C) and CD79a (D).

Kubota T. et al Am J Surg Path Sept 2018

„fluid-overload“ associated lymphoma

- isoliertes Lymphom in Pleuraerguss/Aszites
- keine Immundefizienz
- ältere Erwachsene, oft kardiogene Probleme
- HHV8 und EBV negativ, ass. Hepatitis C
- gute Prognose
- CD20+ oder -; CD20+ bessere Prognose.

ICC: „HHV8 and EBV-negative effusion-based lymphoma“

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Neue Gruppe der „Primary LBCL der immuno-priviledged sites“

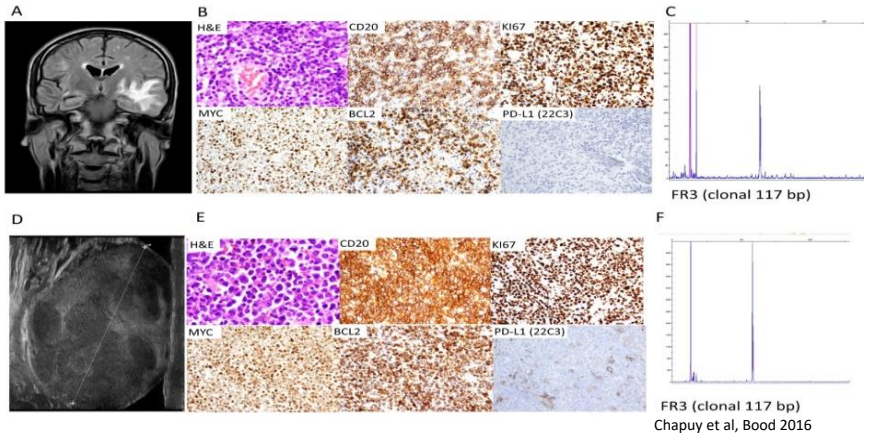
WHOHAEM5: Lymphome der „immunopriviledged sites“

Primäre ZNS-, primär testikuläre und vitroretinale Lymphome zeigen ähnliche (lokotypische?) genetische Merkmale

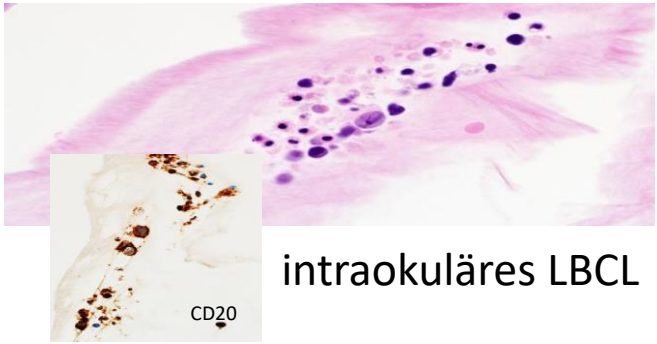
- fortgeschrittenes Lebensalter (>60)
- Organtropismus
- ABC/Non-GCB-Phänotyp
- Hoch rekurrente molek Alterationen: *CD79b* und/oder *MYD88 und Gene der Immunescape (B2M; CIITA; PDL1/2; HLAII)*
- C5/MCD/MYD88 molekulare Signatur

CNS

Testis



Chapuy et al, Bood 2016



intraokuläres LBCL

ICC: „primary DLBCL of the testis/CNS“

WHOHAEM5-Large B-cell lymphomas

Large B-cell lymphomas
Diffuse large B-cell lymphoma, NOS
T-cell/histiocyte-rich large B-cell lymphoma
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
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High-grade B-cell lymphoma, NOS

DLBCL/HGBCL mit *BCL2*- **und** *MYC*-Rearrangement

Sind das alle früheren WHO-„double hit“ Lymphome?

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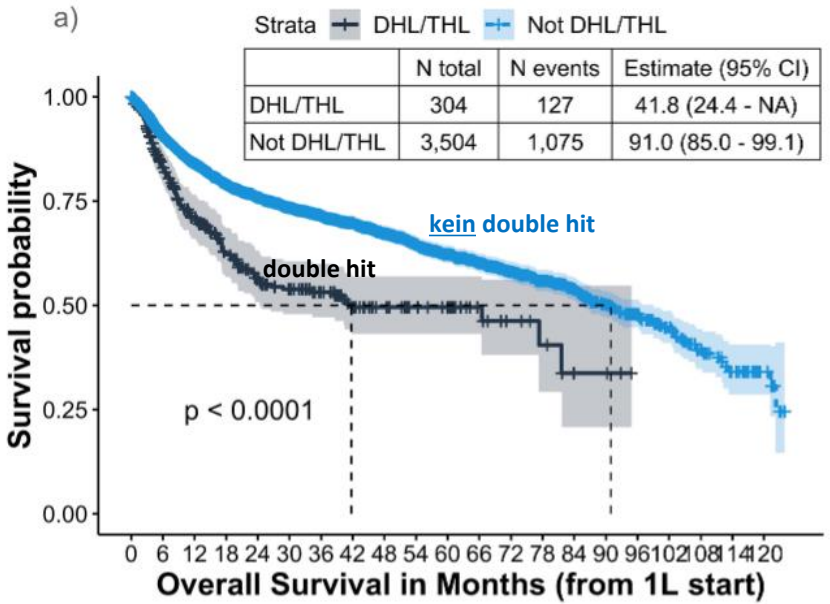
DLBCL/HGBCL mit *BCL2*- **und** *MYC*-Rearrangement

Sind das alle früheren WHO-„double hit“ Lymphome?

WHO 2018: „high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement“

Klinische Relevanz des „molekularen double hit“

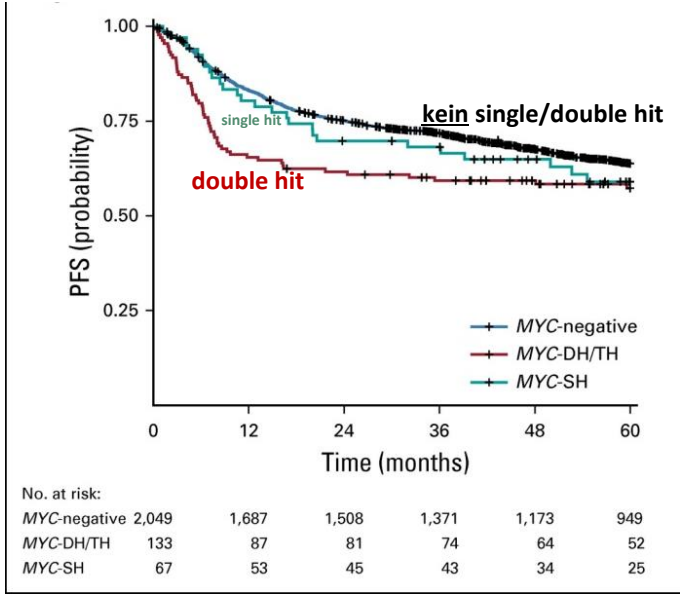


n= 3808 „real world“ DLBCL USA

- 8% double hit
  - -60% MYC and BCL2
  - -20% MYC/BCL2/BCL6
  - -20%MYC/BCL6

Goyal G. et al; Haematologica 2022

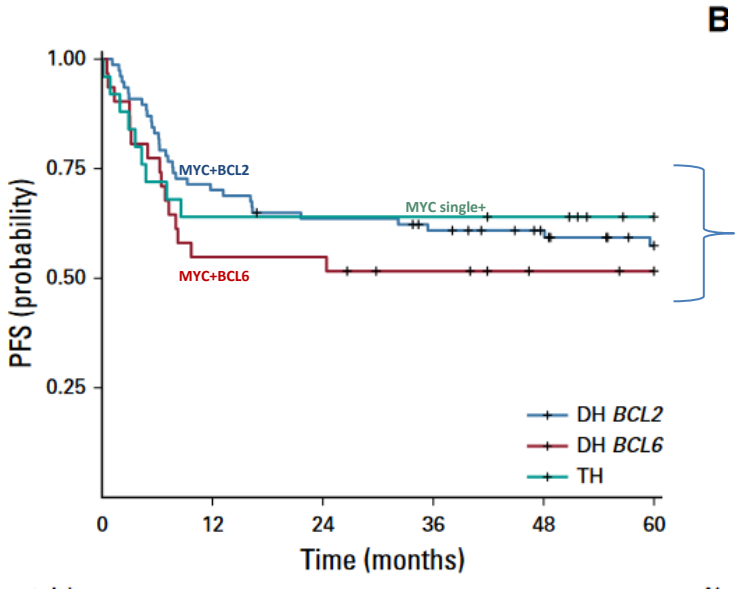
Klinische Relevanz des „molekularen double hit“



R-CHOP/like uniform treatment (**n= 2383 de novo DLBCL** in prospective trials)

Rosenwald A. J Clin Oncol 2019

Klinische Relevanz des „molekularen double hit“

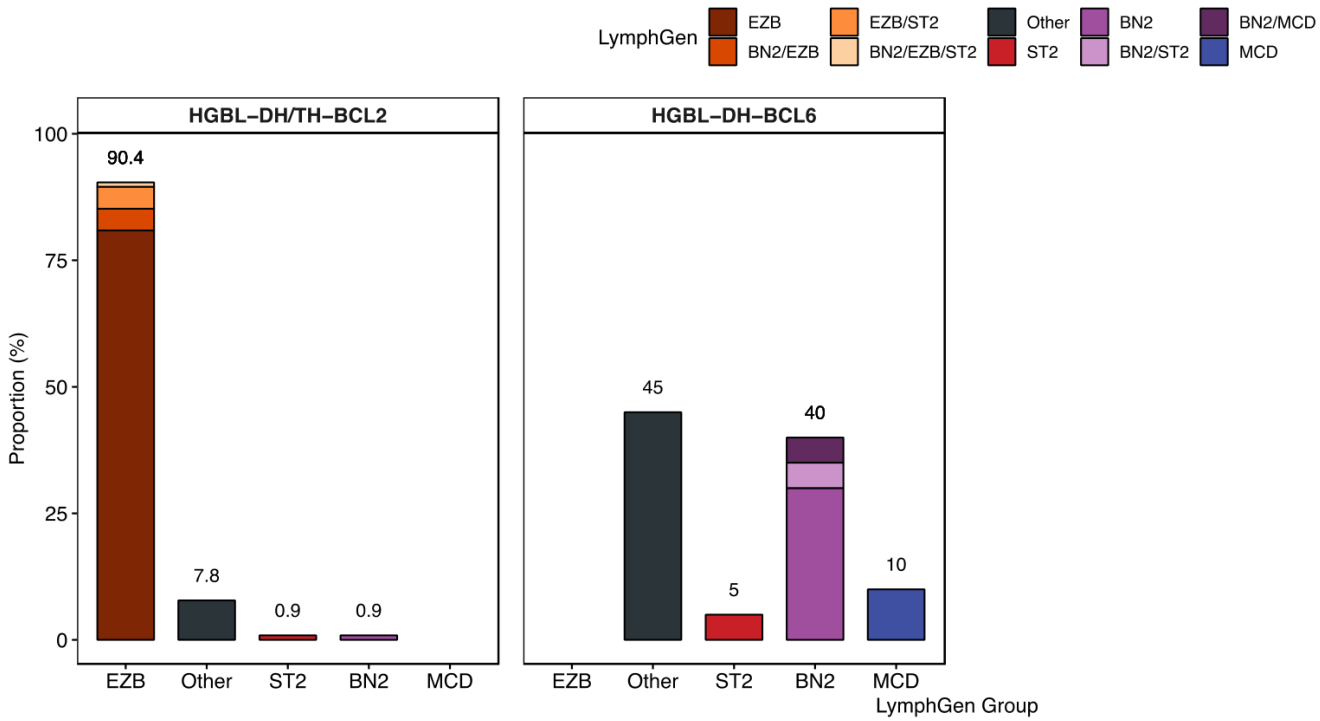


Die 10% der Kohorte **mit** *MYC* Bruch DH/TH

R-CHOP/like uniform treatment (n= 2383 de novo DLBCL in prospective trials)

Rosenwald A. J Clin Oncol 2019

Mutationsprofil der HGBLs mit MYC-double hit



Wright et al Cancer Cell 2020

LLMPP; Unpublished Data

WHOHAEM5-Large B-cell lymphomas

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DLBCL/HGBCL mit *MYC*- **und** *BCL2*-Rearrangement

(ICC: HGBCL mit *MYC*- und *BCL2*-Rearrangement)

- Gruppe der MYC-DH/TH sind prognostisch ungünstiger
- Nur MYC/BCL2 double hit sind molekular homogen

- DLBCL/HGBCL mit DH: MYC/BCL6 bleiben molekulare Subtyp in den DLBCL-NOS, keine Entität.

  (ICC: separate Entität „HGBCL mit MYC und BCL6 R“)

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DLBCL/HGBCL mit *MYC*- **und** *BCL2*-Rearrangement

(ICC: HGBCL mit *MYC*- und *BCL2*-Rearrangement)

- schließt auch TdT+ „doube hit“ Lymphome ein

Bhavsar S. et al; Am J Surg Path 2022

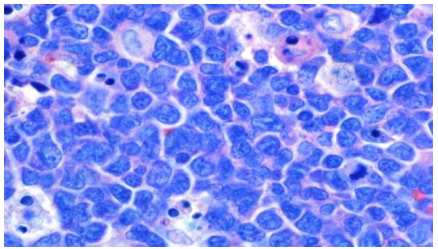
Großzellige B-Zell-Lymphome-WHOHAEM5

(non-Burkitt, non-Precursor, non Mantelzelllymphome)

- DLBCL, NOS (Subtyp mit *MYC/BCL6* double hit)
- *„Andere“* großzellige B-Zell-Lymphome
- High-grade B-Zell Lymphom/DLBCL mit DH/TH
  - definiert über molekulare double hit Konstellation obligat mit ***MYC-*** **und** ***BCL2-Rearrangement*** *(+/-BCL6).*

- High-grade B-Zell Lymphom, NOS: definiert rein morphologisch als „blastoides B-Zell-Lymphom“

  (= DLBCL, NOS mit blastoider Morphologie)



WHOHaem5: HGBL mit „double hit“

Entwicklungsfelder

- Prognostische Signifikanz des *IG* versus *Non-IG* Partners der *MYC-IG* Translokation.
- Typische Eigenschaften der „double-hit“ Lymphome finden sich auch in Teil anderer FISH-negativer DLBCL.
- Rolle der molekular definierten „darkzone“ oder „molekularen high grade“ Signaturen.

Chulin S. J Cin Oncol 2018; Rosenwald A. J Clin Oncol 2019; Alduaijj W. et al Blood 2022

WHOHAEM5-Large B-cell lymphomas
17 spezifische Entitäten

Large B-cell lymphomas
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High-grade B-cell lymphoma, NOS

Morphologie

Molekular definiert

Virus-associated

Lokalisation

Other

WHOHAEM5-DLBCL,NOS

Essential and desirable diagnostic criteria

Essential:

- Large B-cell lymphoma with diffuse or vaguely nodular growth pattern
- Mature B-cell phenotype
- Exclusion of other specific entities of large B-cell lymphoma

Desirable:

- Cell of origin subtyping
- Reporting of isolated *MYC* or dual *MYC* and *BCL6* rearrangements
- Genetic testing, if relevant for clinical decision making

Das DLBCL, NOS bleibt eine Ausschlussdiagnose

WHOHAEM5-DLBCL,NOS

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Das DLBCL, NOS bleibt eine Ausschlussdiagnose

WHC CL,NOS

Essential and desirable diag

Essential:

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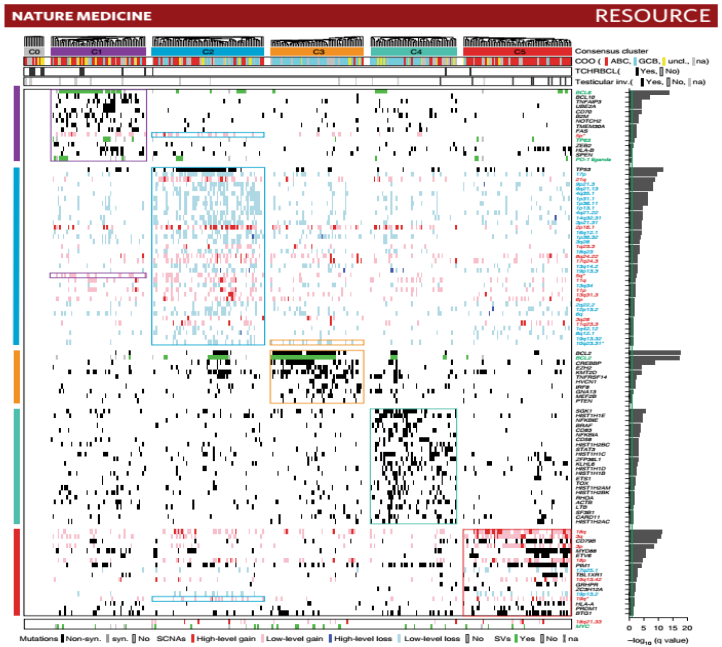
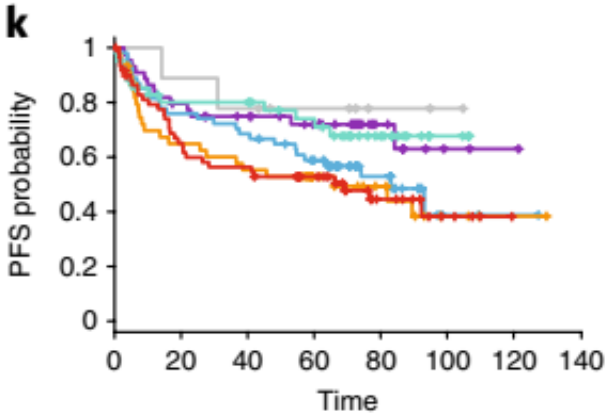
Das DLBCL, NOS bleibt
eine Ausschlussdiagnose

Wie berücksichtigt WHOHAEM5 neuen Daten zur molekularen Subtypisierung der DLBCL, NOS?

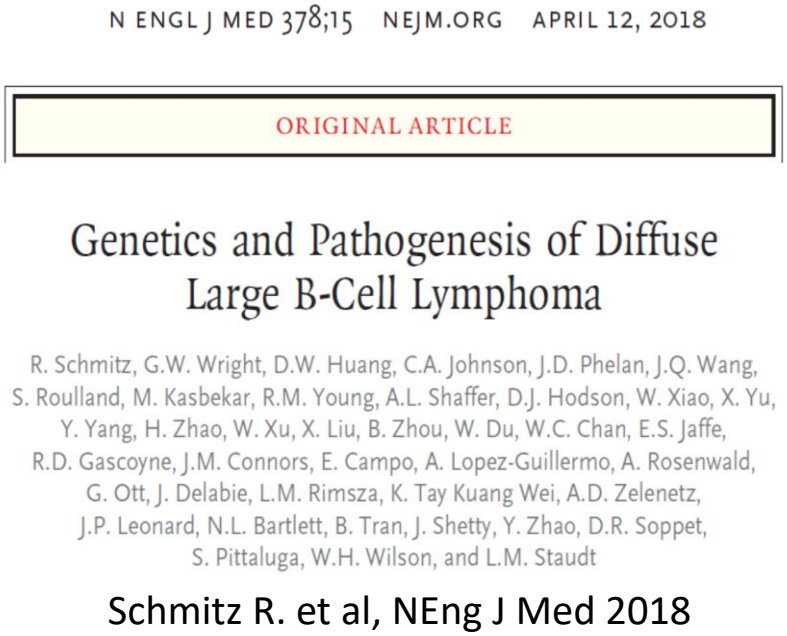


WES -304 de novo DLBCLs- consensus clusters



Chapuy B. et al Nat Med2018

Wie berücksichtigt WHOHAEM5 neuen Daten zu Subtypisierung der DLBCL beyond ABC/GCB?



N ENGL J MED 378;15 NEJM.ORG APRIL 12, 2018

ORIGINAL ARTICLE

Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma

R. Schmitz, G.W. Wright, D.W. Huang, C.A. Johnson, J.D. Phelan, J.Q. Wang, S. Roulland, M. Kasbekar, R.M. Young, A.L. Shaffer, D.J. Hodson, W. Xiao, X. Yu, Y. Yang, H. Zhao, W. Xu, X. Liu, B. Zhou, W. Du, W.C. Chan, E.S. Jaffe, R.D. Gascoyne, J.M. Connors, E. Campo, A. Lopez-Guillermo, A. Rosenwald, G. Ott, J. Delabie, L.M. Rimsza, K. Tay Kuang Wei, A.D. Zelenetz, J.P. Leonard, N.L. Bartlett, B. Tran, J. Shetty, Y. Zhao, D.R. Soppet, S. Pittaluga, W.H. Wilson, and L.M. Staudt

Schmitz R. et al, NEng J Med 2018

<u>weitere</u> prognostisch relevante Subtypisierungen vorgeschlagen

- Wright et al. 2020,
- Lacey et al. 2020,
- Runge et al. 2021...

Lacy et al.	Schmitz et al.	Chapuy et al.
MYD88	MCD	C5
BCL2	EZB	C3
SOCS1/SGK1		C4 (part)
TET2/SGK1		C4 (part)
NOTCH2	BN2	C1

WHOHAEM5 Molekulare Diagnostik im DLBCL, NOS

Despite the overall similar clustering of cases, the lack of consensus in the proposed clusters and their significant genetic drivers precludes the definition of a unified genetic framework of DLBCL, NOS at the present time

Mutational subgroups of DLBCL - The proposed mutational subtypes in DLBCL, NOS have a different impact on prognosis, however there is currently no consensus as to how this additional information might aid in treatment decision making. Clinical trials are required before the clinical utility of the subgroups can be fully elucidated.

Diagnostic molecular pathology

Within the appropriate morphological/immunohistochemical background, exclusion of other entities (*MYC*/*BCL2*, *IRF4*, 11q….) by any cytogenetic/molecular testing is strongly recommended.
Clonality analysis and/or genetic profiling may be helpful, if clinically relevant.
Individual mutation testing (e.g. MYD88) to support diagnosis in difficult cases

WHOHAEM5-DLBCL,NOS

Wie wird der diagnostische Alltag aussehen?

Essential and desirable diagnostic criteria

Essential:

- Large B-cell lymphoma with diffuse or vaguely nodular growth pattern
- Mature B-cell phenotype
- Exclusion of other specific entities of large B-cell lymphoma

Desirable:

- Cell of origin subtyping
- Reporting of isolated *MYC* or dual *MYC* and *BCL6* rearrangements
- Genetic testing, if relevant for clinical decision making

Leitlinie

Diagnostik Onkopedia: Diffus großzelliges B-Zell-Lymphom

- Gewebebiopsie, wenn möglich ganzer LK (auch im Rezidiv)
- Diagnose durch erfahrene/n Hämatopathologen/in
- Anforderung an Routine-Diagnostik
    - CD 20 oder andere B-Marker+
    - Ausschluss MYC-Translokation
    - Cell of Origin (COO) Klassifikation (immun oder molekular)

Fokus auf die häufigsten Entitäten

Was ist neu/anders in der WHOHAEM5?

- Großzellige B-Zell-Lymphome
- Follikuläre Lymphome
- Lymphoproliferationen und Lymphome assoziiert mit Immundefizienz und Immundysregulation

WHOHAEM5: Follikulären Lymphome

UMFRAGE

Berücksichtigen Sie das Grading der Follikulären Lymphome Grad 1, 2, 3A bei Ihren Therapieentscheidungen?

A: Ja

B: Nein

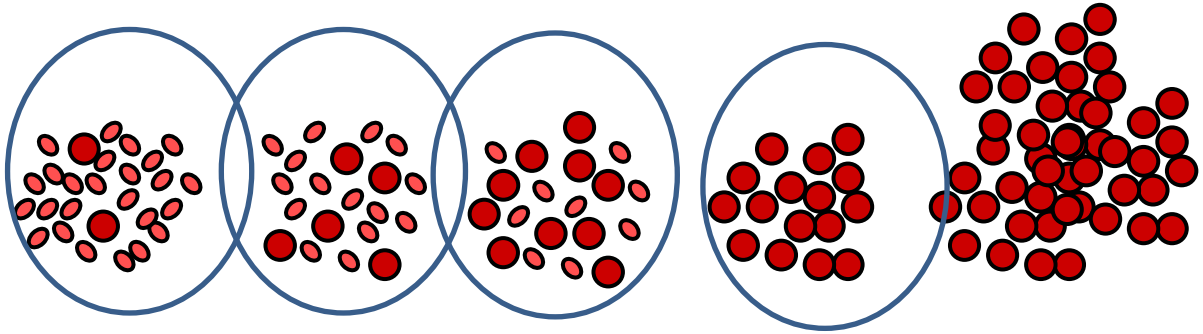
C: Ich weiß nicht.

WHOHAEM5: Follikulären Lymphome

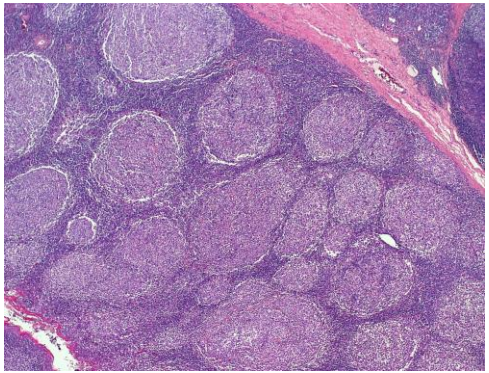
	WHO 2000	WHO2008/16	WHO HAEM5
FL grade 1-3A	+	+	„Classic“ FL (optional grading 1-3A)
FL grade 3B	+	+	Follicular large B-cell lymphoma
			FL with „unusual cytological features“
			FL with diffuse growth
Erkannte lokalisierte Sonderformen des Follikulären Lymphoms mit spez. Klinik/Genetik/Histopath/Mikroenvironment			
„pediatric type“		+	+
„primary cutaneous“*		+	+
„duodenal type“		+	+
„In situ“		+	+

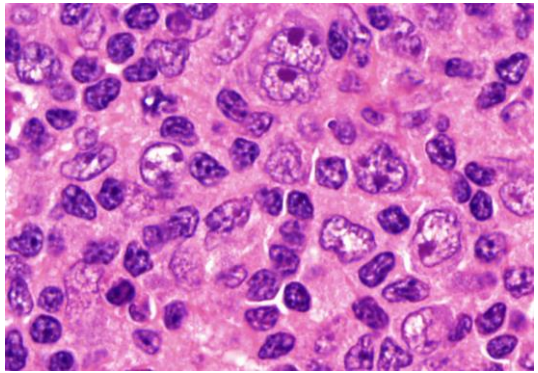
* separierte Entität (aufgrund der Zuordnung zu kutanen Lymphomen)

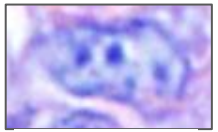
Grading Follikulärer Lymphome



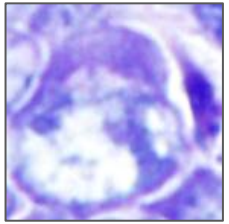
Follikuläres Lymphom Grad 1/2 | Grad 3A | Grad 3B | DLBCL







Centrozyt



Centroblast

Warum wird (*endlich*) das Grading FL 1-3A verlassen?

- Blastenanzahl/HPF ist ein schlechtes definierendes Kriterium
- Schlechte Reproduzierbarkeit

Rimsza L., Haematol 2018; Kroft S, Am J Clin Path 2019; Koch K. Ann Oncol 2016

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Rimsza L., Haematol 2018; Kroft S, Am J Clin Path 2019; Koch K. Ann Oncol 2016

Warum wird (*endlich*) das Grading FL 1-3A verlassen?

- Blastenanzahl/HPF ist ein schlechtes definierendes Kriterium
- Schlechte Interobserver-Reproduzierbarkeit

- Unter aktuellen Therapien zeigt sich **kein signifikanter Einfluss** des Gradings (1-3a) auf das outcome.

- Häufiges Nebeneinander FL1-3a in einem Lymphknoten.
- Molekulare Ähnlichkeit der Lymphome in der Gruppe FL1-3a.

Whalin Haematol 2018; Rimsza L., Haematol 2018; Kroft S, Am J Clin Path 2019; Bachy E., J Clin Oncol 2019; Laurent LC Am J Surg Path 2021; Hiddemann W., J Clin Oncol 2018; Koch K. Ann Oncol 2016

Warum achtet die Pathologie dennoch auf die Zytologie?

- Auffällige Zytologie/Höherer Blastengehalt kann Schlüssel zu Sonderformen der Follikulären Lymphome sein, z.B. „FL3U“*.
- Zytologie kann auf Differentialdiagnose hinweisen.
- Zytologie ist wesentlich für DD zu reaktiver follikulärer Hyperplasie

*Laurent C. et al; Am. J Surg Path. 2021

Warum wird das FL3B zum Follikulären großzelligen B-Zell-Lymphom umbenannt?

Ist das FL3B klinisch näher am DLBCL als am FL 1-3a?

Bislang konnte ein unterschiedlicher klinischer Verlauf unter Therapie zwischen FL3A versus FL3B nicht klar belegt werden.

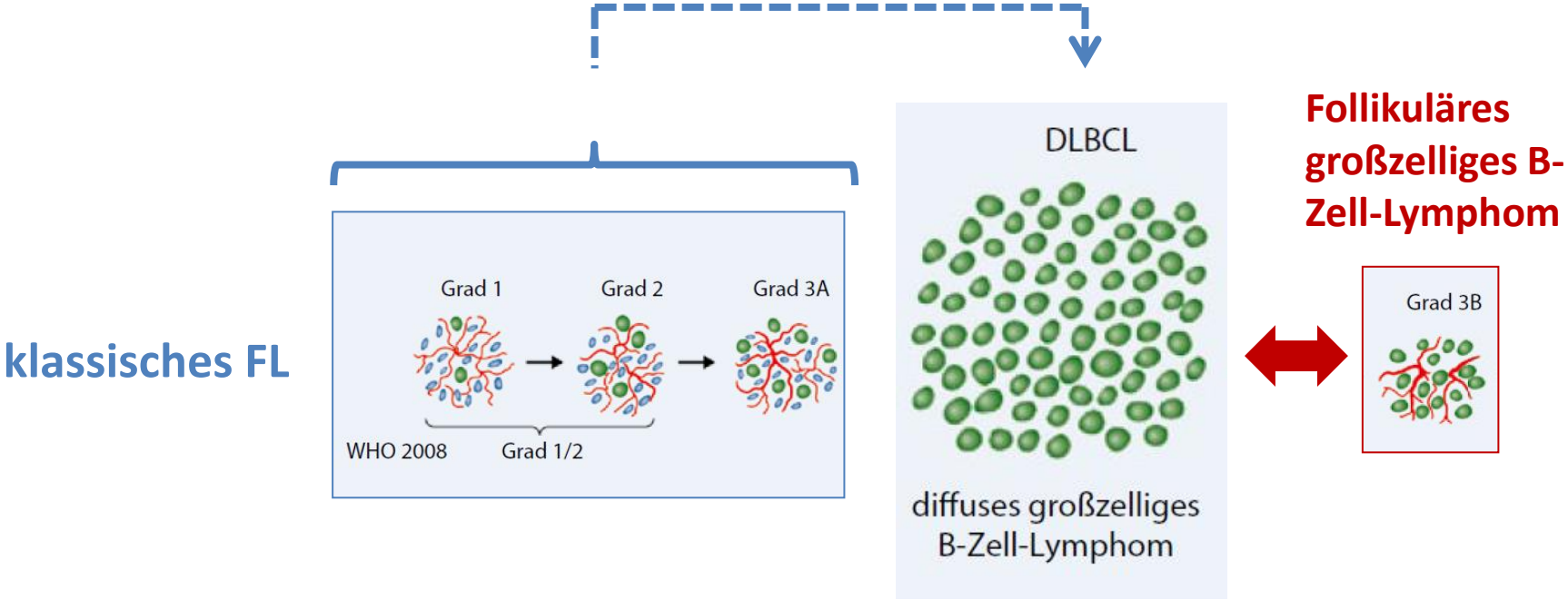
Hsi et al. Arch Pathol Lab Med 2004; Shustik et al. Ann Oncol 2010; Wahlin et al. Br J Haematol 2011; Koch et al Ann Oncol 2016

Warum wird das FL3B zum Follikulären großzelligen B-Zell-Lymphom umbenannt?

- Molekular verschieden von FL1-3a und ähnlich den DLBCL, GCB.
- Häufiges Nebeneinander FL3B und DLBCL in einem Lymphknoten, aber seltenes Nebeneinander von FL3B mit FL1-3a.
- FL3B mit oder ohne simultanes DLBCL unterscheiden sich weder molekular noch klinisch.

Horn H. et al, Haematologica 2011; Horn H. et al. Haematol 2018; Koch K. et al., Haematologica 2022

Warum wird das FL3B zum Follikulären großzelligen B-Zell-Lymphom umbenannt?



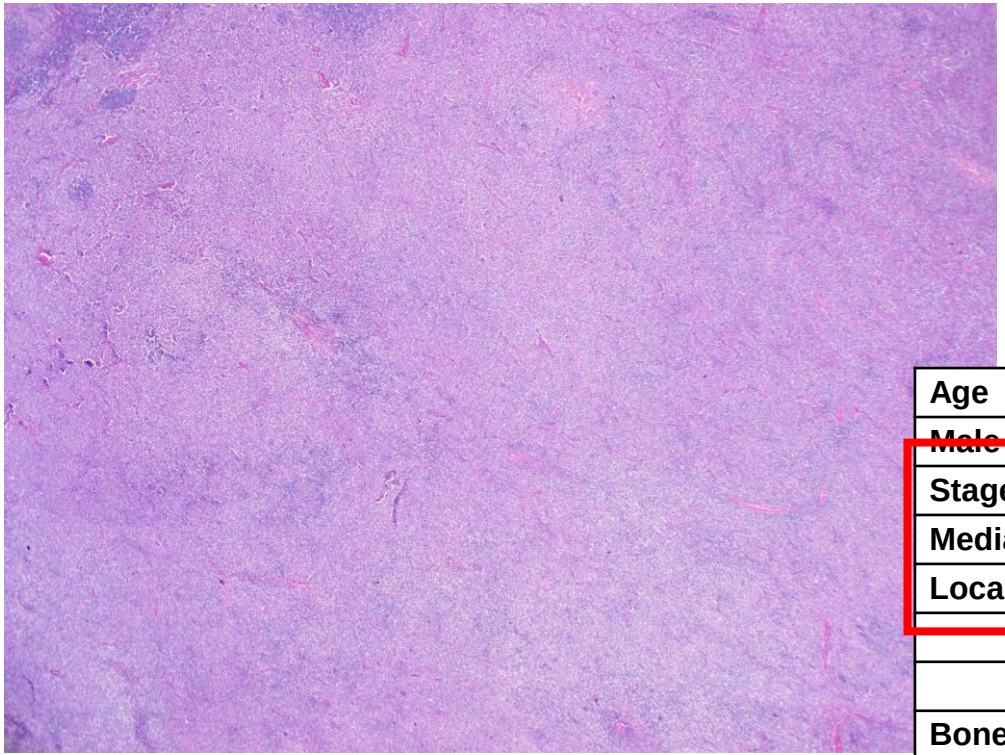
WHOHAEM5: uFL „with unusual cytological features“

- Zytologie „blastoid“-intermediär zwischen Centrozyt und Centroblast
- höhere Proliferation
- oft negativ für *BCL2*-Translokation

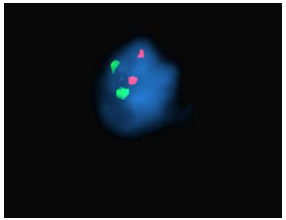
...“*fast ein FL 3B....aber eben kein typisches FL3B*“-klinisch-pathologische Korrelation hilfreich.

WHOHAEM5: neuer „diffuser Subtyp“ des FL

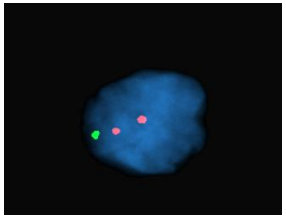
(ICC: „BCL2-R-negative,CD23-positive follicle centre lymphoma“)



häufig: *STAT6* Mutation, CD23 positiv



IGH::BCL2 negativ



1p23 deletion

Age	**57 (27-85)**
Male gender	**51%**
Stage I/II	**75%**
Median tumor size	**4 cm**
Localisation	**83% inguinal**
	9% cervical
	9% axillär
Bone Marrow Infiltration	**5%**
Primary Diagnoses	**97%**

Katzenberger T. et al. Blood 2009; Zamo A. et al, Br J Haemtaol 2019; Nann D. et al; Blood Adv 2020;

WHOHAEM5-Follikuläre Lymphome

Wie wird der diagnostische Alltag aussehen?

Essential and desirable diagnostic criteria

Essential:

B-cell lymphoma composed of varying proportions of centrocytes (CC) and/or centroblasts (CB)/large transformed cells, with the dominance of CC in the overwhelming majority of cases.

Immunophenotype compatible with germinal center B-cell origin with positivity to markers such as CD10, BCL6, MEF2B, GCET1, GCET2 or LMO2

Desirable:

At least partly follicular growth pattern

BCL2 or *BCL6* rearrangements and/or lack of *IRF4* rearrangement (in equivocal cases)

Leitlinie

Diagnostik Onkopedia: Follikuläres Lymphom-Stand April 2023

- Gewebebiopsie , wenn möglich ganzer Lymphknoten
- Diagnose durch erfahrene/n Hämatopathologen/in empfohlen
- <u>Anforderung an Routine-Diagnostik</u>
    - Differenzierung „klassischer Typ“ des FL (1-3A) versus „großzelliges (3B) Follikuläres B-Zell-Lymphom“

Fokus auf die häufigsten Entitäten

Was ist neu/anders in der WHOHAEM5?

- Großzellige B-Zell-Lymphome
- Follikuläre Lymphome

- Lymphoproliferationen und Lymphome assoziiert mit Immundefizienz und Immundysregulation

Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation

- WHO 2000-2016 benannte Entitäten assoziiert zu speziellen Arten der Immunsuppression, z.B. PTLD/HIV/MTX/PID.
  Problem: nicht alle Formen der Immunsuppression sind abgedeckt!

Spektrum der Diagnosen in ~50 PID-assoziierten Fällen*

Table 2
Primary Immunodeficiency-Related Cases Submitted to the Workshop Cover the Full Spectrum of B-Cell Lymphoproliferative Disease[a]

Characteristic	Hyperplasia	MCU	Low-Grade Lymphoma	Polymorphic B-cell LPD	CHL	DLBCL	Burkitt	Plasma-blastic
Immune dysregulation	ALPS XLP			Chédiak-Higashi[b] XLP[b]		Chédiak-Higashi[b]	XLP (2)	Wiskott[b]
DNA repair			AT[b] Nijmegen[b]	Bloom[b]	Nijmegen[b]	AT (2) CMRD Nijmegen		
Low immunoglobulin	CVID (5) PIKC3D		CVID (2)	CVID (2,6[b])	CVID[b]	CVID (2,2[b]) IgSD (2[b]) PIKC3D[b]		
Combined immunodeficiency		CHARGE[b]		CHARGE[b] DOCK8[b]		Δ22q11.2[b] SCID (2[b])		

* Gratzinger D. et al SH/EAHP workshop report; Am J Clin Path 2017

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b = EBV positive

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  Problem: nicht alle Formen der Immunsuppression sind abgedeckt!
- Jede Form der ID kann variable Lymphoproliferationen/Lymphome bedingen.
- Nicht alle LPDs treten bei jeder Form der ID auf.
- Der Pathologe kann in der Regel die zugrundeliegende ID nicht erkennen.
- *Die EBV Assoziation ist häufig aber variabel.*

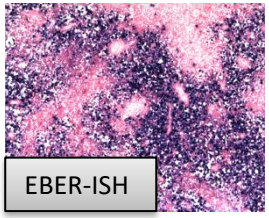
Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation

Hyperplasias arising in immune deficiency/dysregulation
Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation
EBV-positive mucocutaneous ulcer
Lymphomas arising in immune deficiency / dysregulation
Inborn error of immunity-associated lymphoid proliferations and lymphomas

WHOHAEM5

3 Bausteine für eine korrekte Diagnose

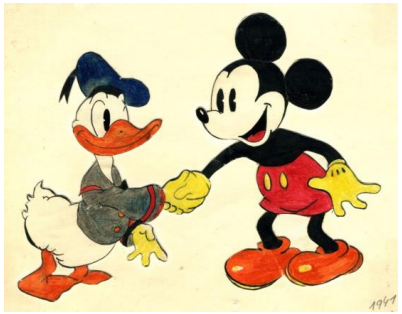
Histopathologie	Art des Immundefektes	Virus
• Hyperplasie •Polymorphic LPD •EBV MCU •Lymphom	• inborn error • iatrogenic •acquired HIV • post TX (solid or BM) • immuno senescence	• EBV • HHV8/KSH



WHOHAEM5

Ein kontinuierliches Grundprinzip: essentielle klinische Angaben beeinflussen die Klassifikation

- Alter
- Manifestationsort. Lokalisierter oder generalisierter Prozess?
- Tumorverdacht oder Zufallsbefund?
- Immunsuppression/Dysregulation/Syndrom
- Anamnese eines Lymphoms, Transformation?
- Relevante Therapien?

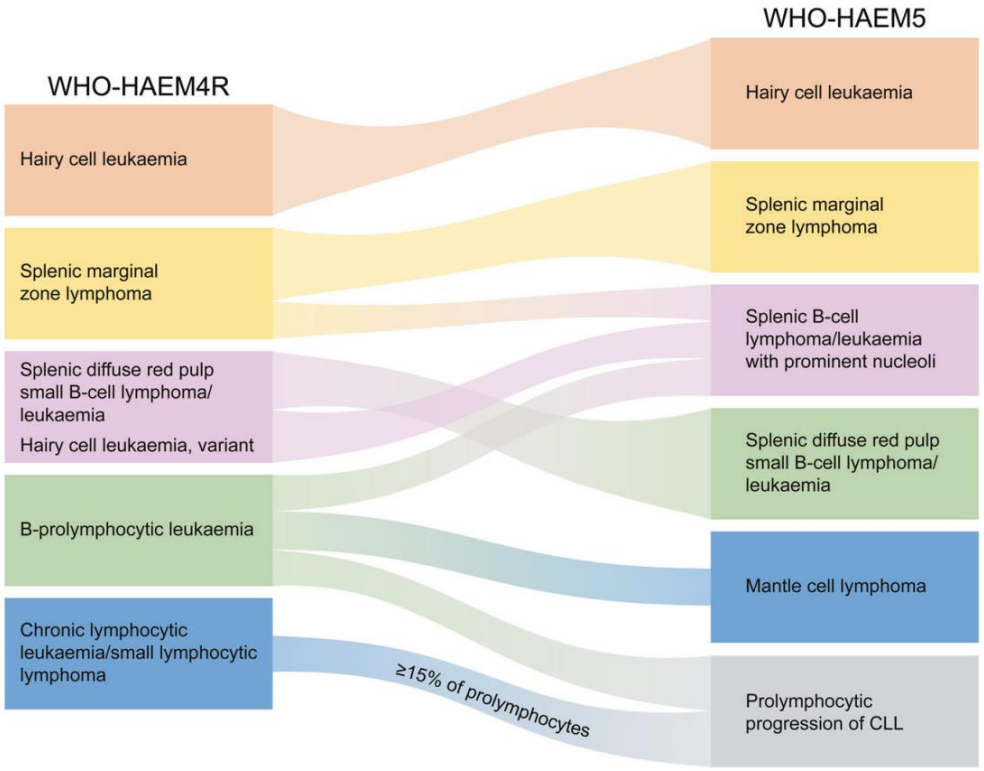


Vielen Dank!

Prof. Dr. German Ott
Prof. Dr. Wolfram Klapper
Prof. Dr. Reiner Siebert

Danke an alle anwesenden Onkolog*Innen für das Vertrauen und die
enge klinisch-pathologische Zusammenarbeit.

Bewegung bei den splenischen Lymphomen



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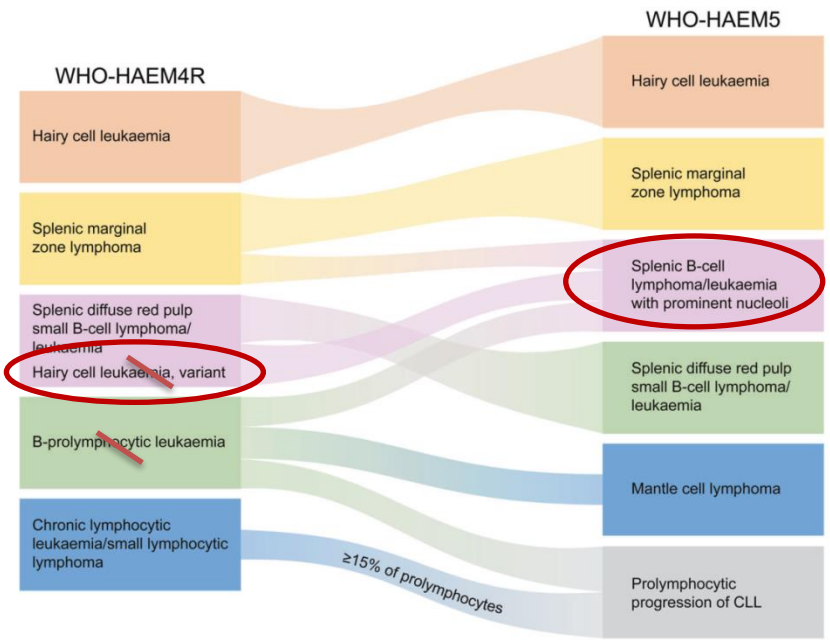
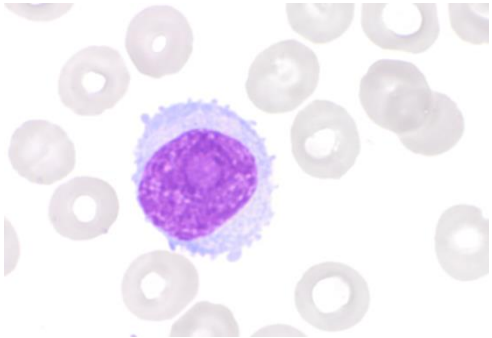
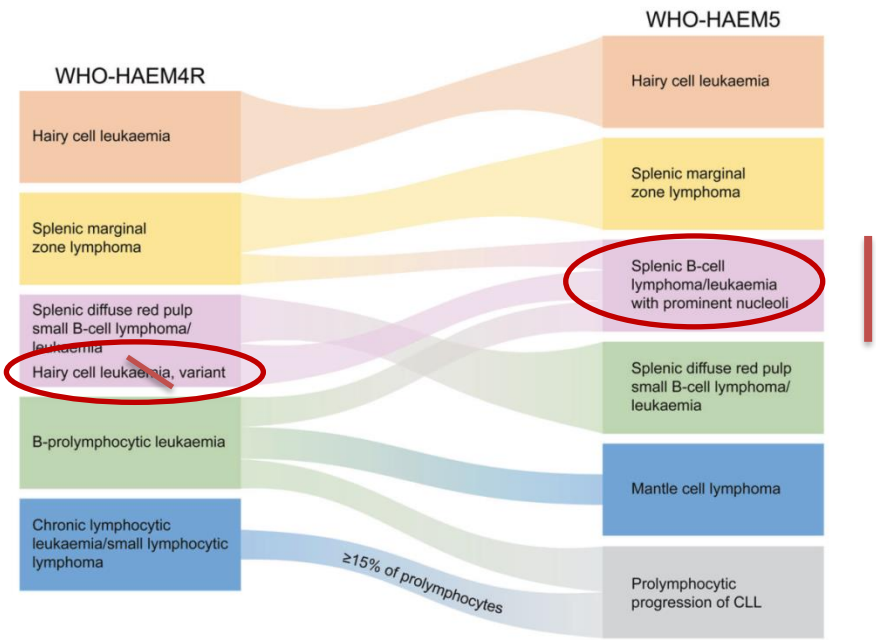


SELTEN: „Splenic B-cell lymphoma/leukemia with prominent nucleoli“

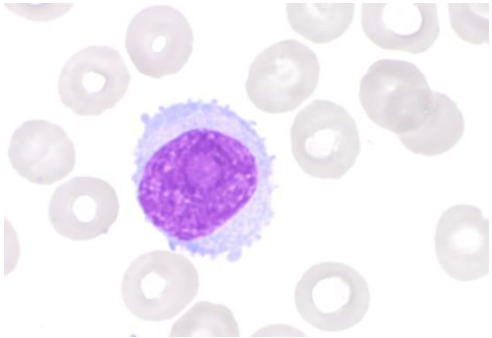


- Diagnose nach Ausschluss
  - Mantelzelllymphom
  - Prolymphozytenreiche Progression der CLL
  - Typische Haarzellenleukämie

Bewegung bei den splenischen Lymphomen

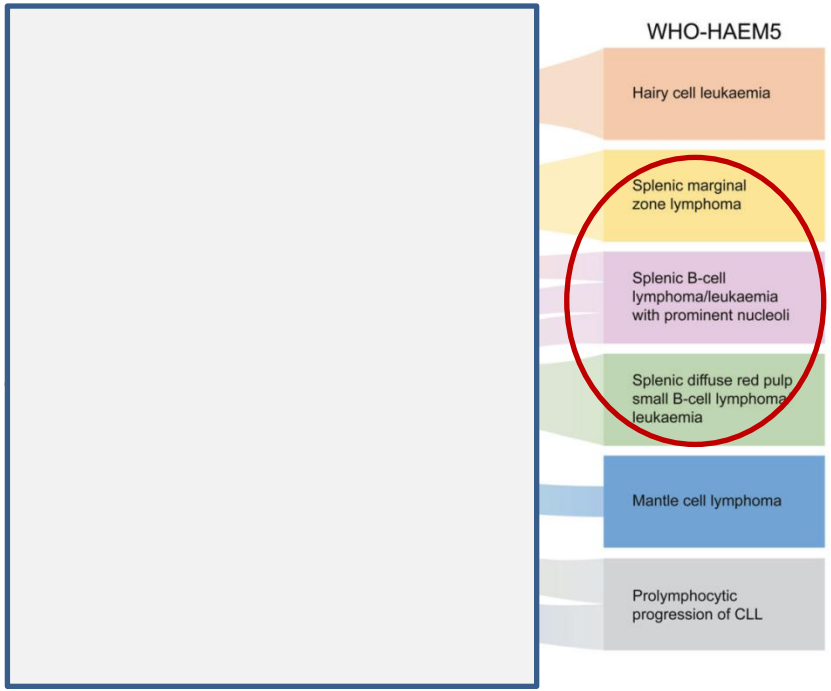


Neu: Splenic B-cell lymphoma/leukemia with prominent nucleoli



- ähnelt der HZL (Milzbefall, Leukämie)
- aggressiver, resistent gegen HZL-Therapie
- keine BRAF (oder MAP2K) Mutation
- FACS Profil ähnl. (CD25-, TRAP-, Ann-, Cd123-, CD103+/-)
- KM-Infiltrationspattern anders

Bewegung bei den splenischen Lymphomen



Schwierige DD der splenischen Lymphome nach Ausschluss HZL, MCL, CLL....

- Überschneidende klinische, immunphänotypische und molekulare Veränderungen
- Typische Zytologie separiert SBPLN
- Nur das Infiltrationsmuster in Milz ist bestimmend

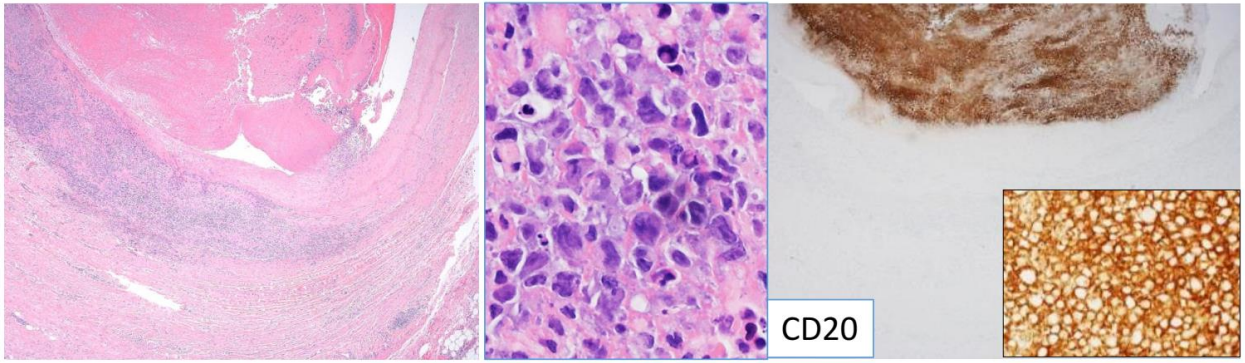
Das „splenisches MZL-NOS“ wird eine häufige Diagnose bleiben.

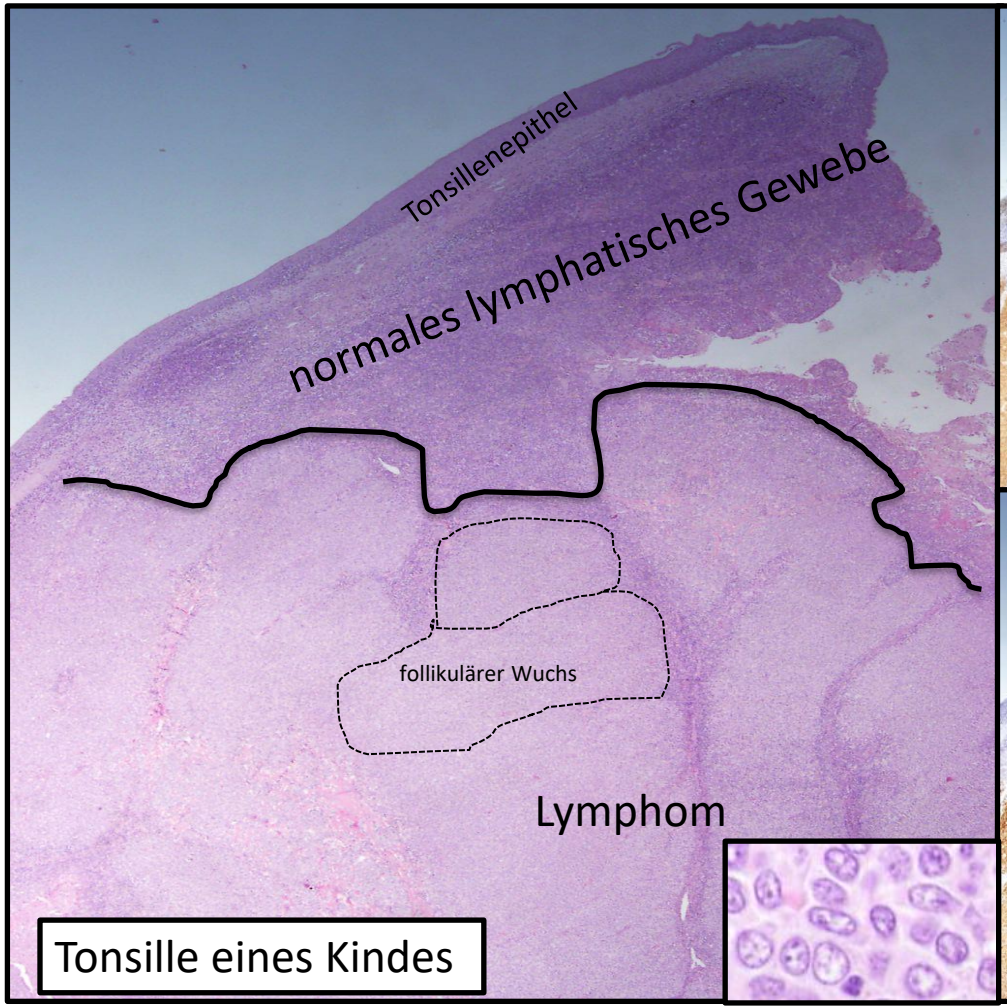
WHOHAEM5-Large B-cell lymphomas: Neue Entität des „fibrin-assoziieren“ Lymphoms

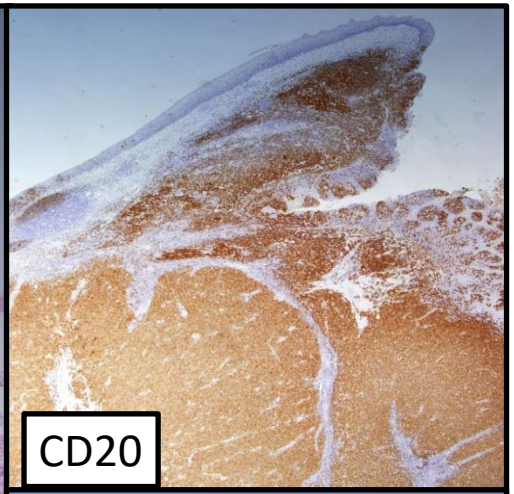
„fibrin-associated large B-cell lymphoma“

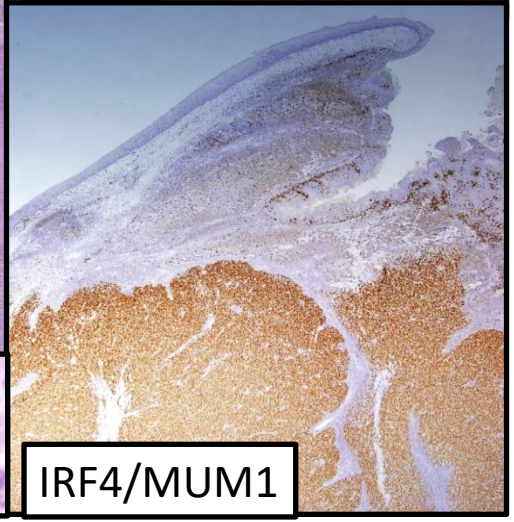
- lokalisiert, kein Tumor, in der Regel ein Zufallsbefund
- Fibrincluster mit dichten B-Blasten
- meist EBV+
- keine Systemtherapie nötig

Case 183 Dr. McPhail **FA-DLBCL** (with aortic aneurysm)









Großzelliges B-Zell Lymphom mit IRF4-Translokation (LBCL *IRF4*r)

Fallbeispiel

Leitlinie

Umfrage 1: Lesen von pathologischen Befunden

Ihre Patientin:

- **45 j. Frau, langjährige Colitis ulcerosa unter immunsuppressiver Therapie**
- **Großer inguinaler Tumor, LDH erhöht, B-Symptome, V.a. Lymphom**

- **LK Exzision. der Pathologe/in sendet seinen Befund.**

Fallbeispiel

Leitlinie

Lesen von pathologischen Befunden

Der Befund:

„Komplett aufgehobene LK-Grundstruktur. Rasen CD20+ Blasten mit Zytologie von Immunoblasten und Zentroblasten. Keine Expression von Cyclin D1 oder TdT. MYC stark exprimiert.
CD10-, Mum1+, Ki67 90%; wenige CD3-positive T-Zellen untermengt.“

Diagnose: Lymphknoten inguinal mit Infiltraten eines Diffus großzelliges B-Zell-Lymphom, Non-GCB-Subtyp.

Umfrage

Leitlinie

Was würden Sie jetzt machen?

A Ich hefte den Befund sorgfältig ab und behandle den Patienten leitliniengerecht als DLBCL.

B Ich führe ein freundliches Telefonat mit dem Befunder und bitte um eine korrekte Nomenklatur unter Berücksichtigung der mutmaßliche iatrogenen Immunsuppression.

C Ich bitte freundlich um Nachbestimmung des EBV-Status des Lymphoms.

D Ich bitte um eine Untersuchung des MYC-Translokationsstatus.

E Alle Antworten B-D sind korrekt.

Leitlinie

Umfrage 2: Klassifikation der Großzelligen B-Zell-Lymphome

Welche Zuordnung ist korrekt?

A Diffuses Follikuläres Lymphom - aggressiv, t(14::18) positiv.

B Großzelliges B-Zell-Lymphom der „immunopriviledged site“ - junge Patienten, nodal.

C High grade B-Zell-Lymphom, NOS - „double hit“ für MYC und BCL2.

D Blastoide Morphologie - assoziiert mit „high-grade“; Blasten mittlerer Größe.

E Transformation - Übergang Follikuläres Lymphom Grad 2 in Grad 3a

WHOHAEM5 Molekulare Diagnostik im DLBCL, NOS

Molecular Subtypes

Cell-of-origin centered

Germinal center B-cell-like

- GC immunophenotype
- mutational spectrum related to drivers of GC development, DZ/LZ transitions, microenvironmental interactions

Activated B-cell- like

- post-GC immunophenotype
- mutational spectrum related to BCR pathway mutations/NFkB drivers

Genetic Subtype *(new)*

- DLBCL, NOS with rearrangements of *MYC* and *BCL6*

Diagnostic molecular pathology

Within the appropriate morphological/immunohistochemical background, exclusion of other entities (*MYC*/*BCL2*, *IRF4*, 11q….) by any cytogenetic/molecular testing is strongly recommended.
Clonality analysis and/or genetic profiling may be helpful, if clinically relevant.
Individual mutation testing (e.g. MYD88) to support diagnosis in difficult cases