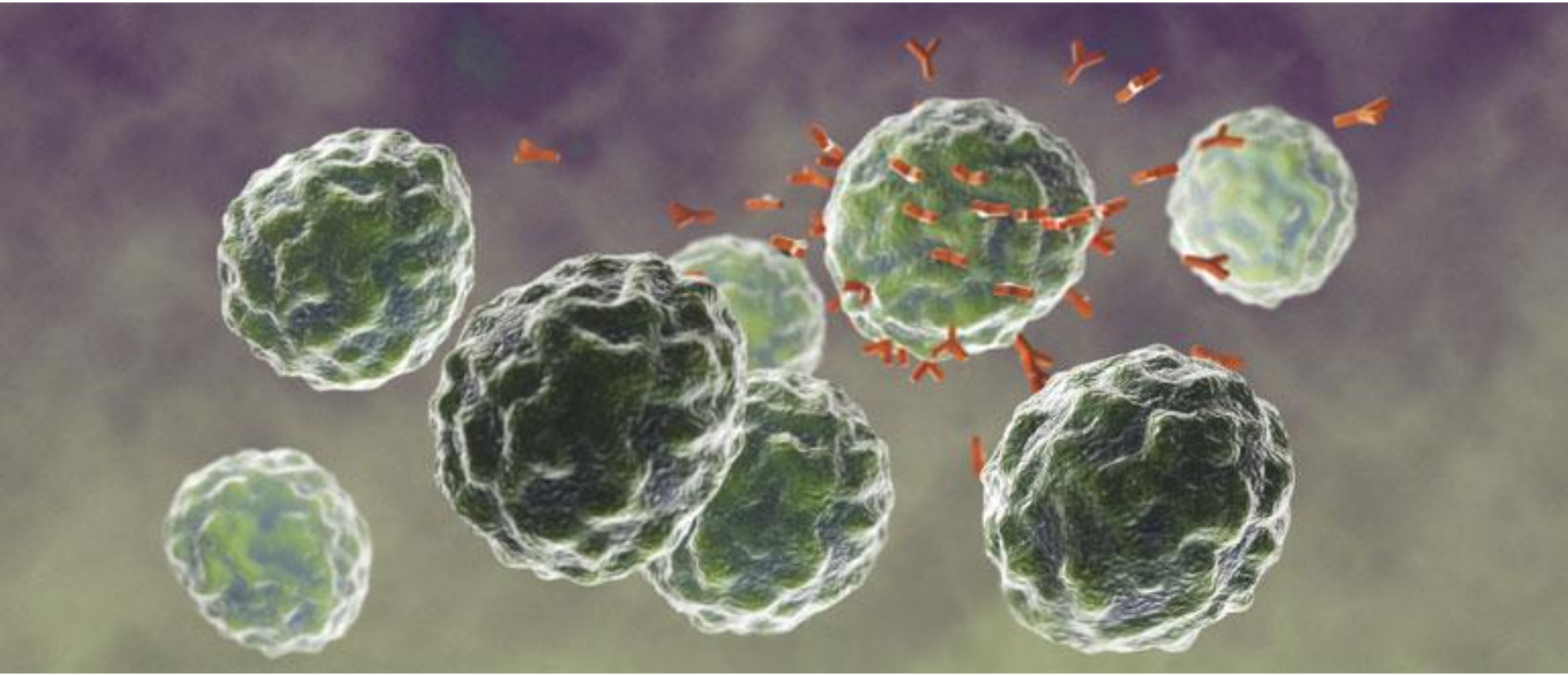
Mature B-cel neoplasmata



Goda Choi / C.W.Choi@umcg.nl

Mature B-cell neoplasmata (WHO 5)

Leukemia

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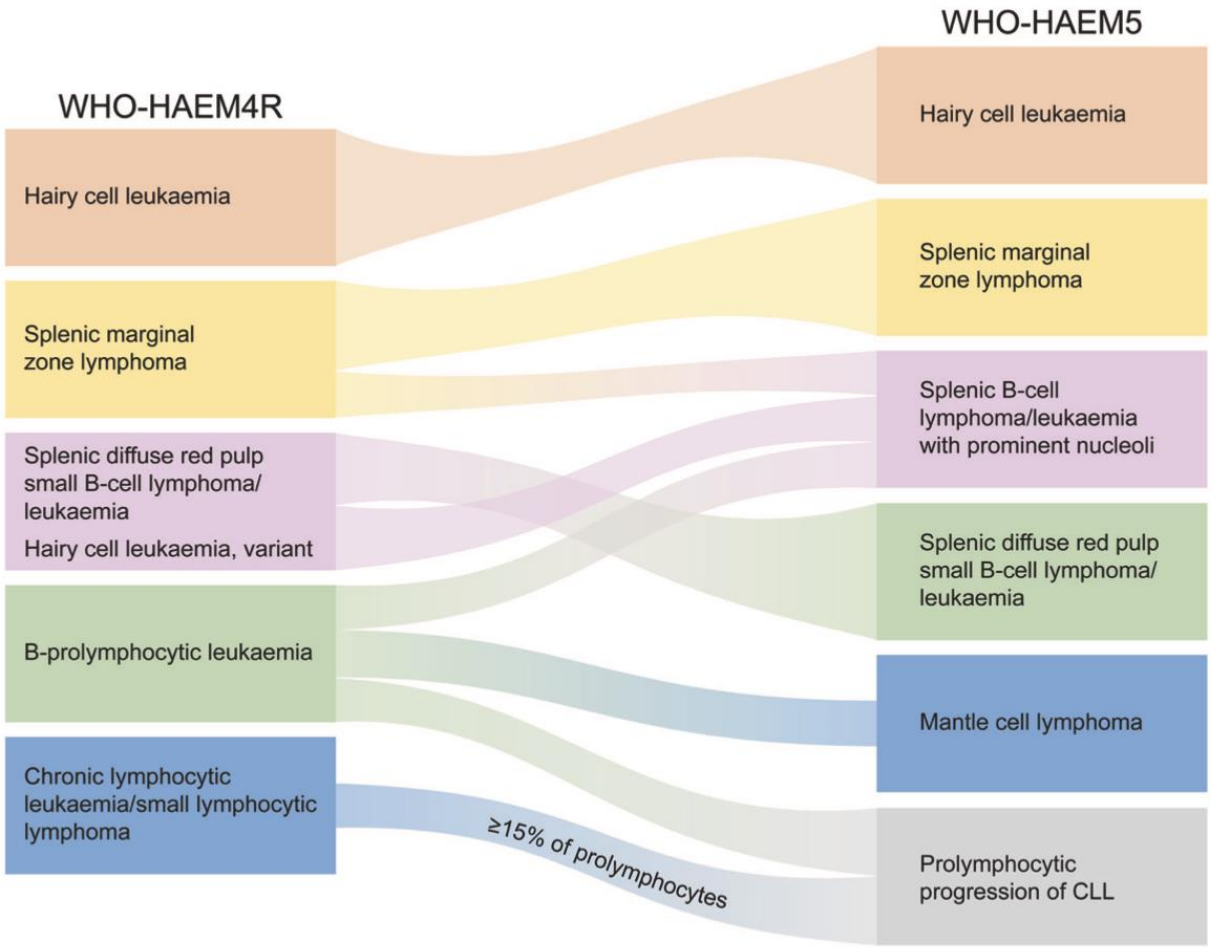
LYMPHOMA

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[12], 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]✉, Kojo S. Elenitoba-Johnson[21], Judith Ferry[22]✉, Julia Geyer[11], Dita Gratzinger[23], Joan Guitart[24], Sumeet Gujral[25], Marian Harris[26], Christine J. Harrison[27], Sylvia Hartmann[28], Andreas Hochhaus[29], Patty M. Jansen[30], Kennosuke Karube[31], Werner Kempf[32], Joseph Khoury[33], Hiroshi Kimura[34], Wolfram Klapper[35], Alexandra E. Kovach[36], Shaji Kumar[37], Alexander J. Lazar[38], Stefano Lazzi[39], Lorenzo Leoncini[39], Nelson Leung[40], Vasiliki Leventaki[41], Xiao-Qiu Li[42], Megan S. Lim[21], Wei-Ping Liu[43], Abner Louissaint Jr.[22], Andrea Marcogliese[44], L. Jeffrey Medeiros[33], Michael Michal[45], Roberto N. Miranda[33], Christina Mitteldorf[46], Santiago Montes-Moreno[47], William Morice[48], Valentina Nardi[22], Kikkeri N. Naresh[49], Yasodha Natkunam[23], Siok-Bian Ng[50], Ilske Oschlies[35], German Ott[51]✉, Marie Parrens[52], Melissa Pulitzer[53], S. Vincent Rajkumar[54], Andrew C. Rawstron[55], Karen Rech[48], Andreas Rosenwald[3], Jonathan Said[56], Clémentine Sarkozy[57], Shahin Sayed[58], Caner Saygin[59], Anna Schuh[60], William Sewell[61], Reiner Siebert[62]✉, Aliyah R. Sohani[22], Reuben Tooze[63], Alexandra Traverse-Glehen[64], Francisco Vega[33], Beatrice Vergier[65], Ashutosh D. Wechalekar[66], Brent Wood[36], Luc Xerri[67] and Wenbin Xiao[53]

Mature B-cell neoplasmata (WHO 5)



Alaggio. *Leukemia* 2022

Mature B-cell neoplasmata (ICC)

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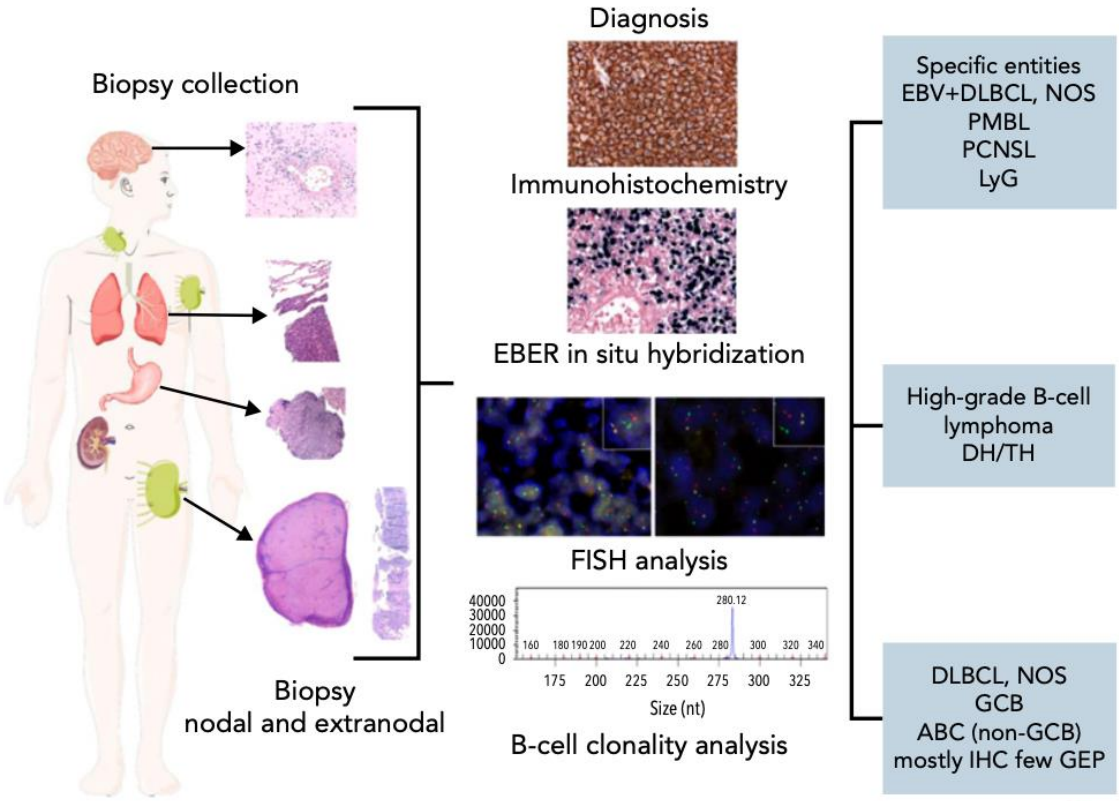
The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

Elias Campo,[1] Elaine S. Jaffe,[2] James R. Cook,[3] Leticia Quintanilla-Martinez,[4] Steven H. Swerdlow,[5] Kenneth C. Anderson,[6] Pierre Brousset,[7] Lorenzo Cerroni,[8] Laurence de Leval,[9] Stefan Dirnhofer,[10] Ahmet Dogan,[11] Andrew L. Feldman,[12] Falko Fend,[4] Jonathan W. Friedberg,[13] Philippe Gaulard,[14,15] Paolo Ghia,[16] Steven M. Horwitz,[17] Rebecca L. King,[12] Gilles Salles,[17] Jesus San-Miguel,[18] John F. Seymour,[19] Steven P. Treon,[6] Julie M. Vose,[20] Emanuele Zucca,[21] Ranjana Advani,[22] Stephen Ansell,[23] Wing-Yan Au,[24] Carlos Barrionuevo,[25] Leif Bergsagel,[26] Wing C. Chan,[27] Jeffrey I. Cohen,[28] Francesco d'Amore,[29] Andrew Davies,[30] Brunangelo Falini,[31] Irene M. Ghobrial,[6,32] John R. Goodlad,[33] John G. Gribben,[34] Eric D. Hsi,[35] Brad S. Kahl,[36] Won-Seog Kim,[37] Shaji Kumar,[23] Ann S. LaCasce,[6] Camille Laurent,[7] Georg Lenz,[38] John P. Leonard,[39] Michael P. Link,[40] Armando Lopez-Guillermo,[41] Maria Victoria Mateos,[42] Elizabeth Macintyre,[43] Ari M. Melnick,[44] Franck Morschhauser,[45] Shigeo Nakamura,[46] Marina Narbaitz,[47] Astrid Pavlovsky,[48] Stefano A. Pileri,[49] Miguel Piris,[50] Barbara Pro,[51] Vincent Rajkumar,[12] Steven T. Rosen,[52] Birgitta Sander,[53] Laurie Sehn,[54] Margaret A. Shipp,[6] Sonali M. Smith,[55] Louis M. Staudt,[56] Catherine Thieblemont,[57,58] Thomas Tousseyn,[59] Wyndham H. Wilson,[56] Tadashi Yoshino,[60] Pier-Luigi Zinzani,[61] Martin Dreyling,[62] David W. Scott,[54] Jane N. Winter,[63] and Andrew D. Zelenetz[17,64]

Campo. *Blood* 2022

Advanced diagnostics



Campo. *Blood* 2022

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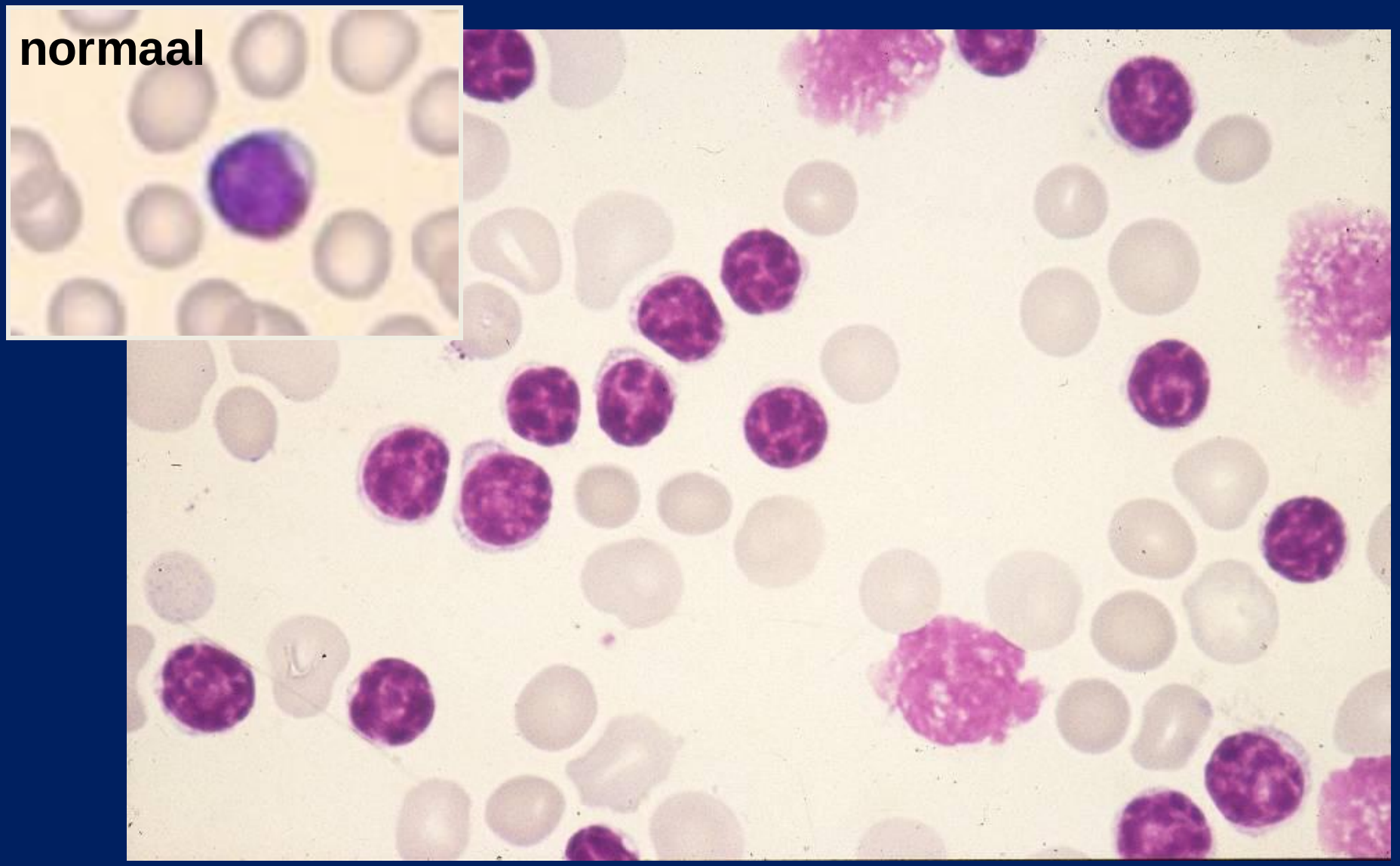
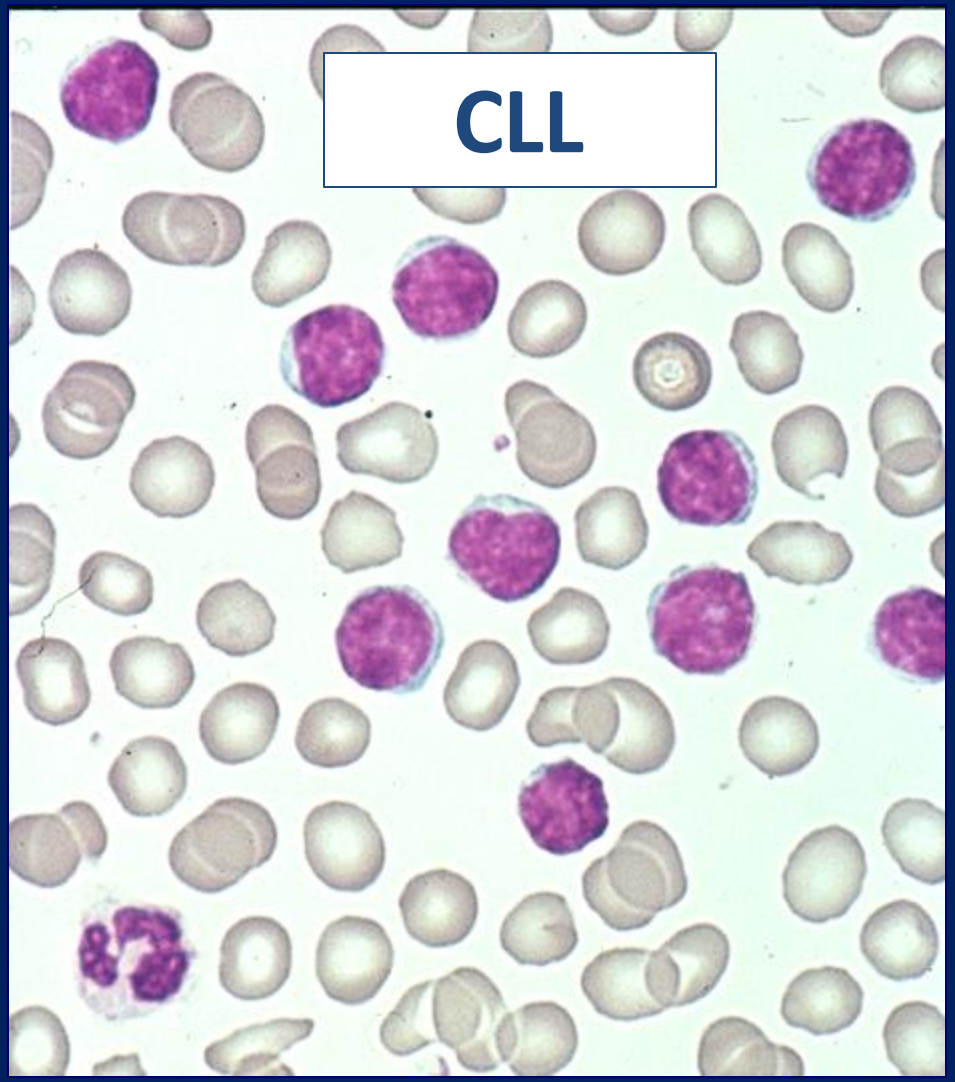
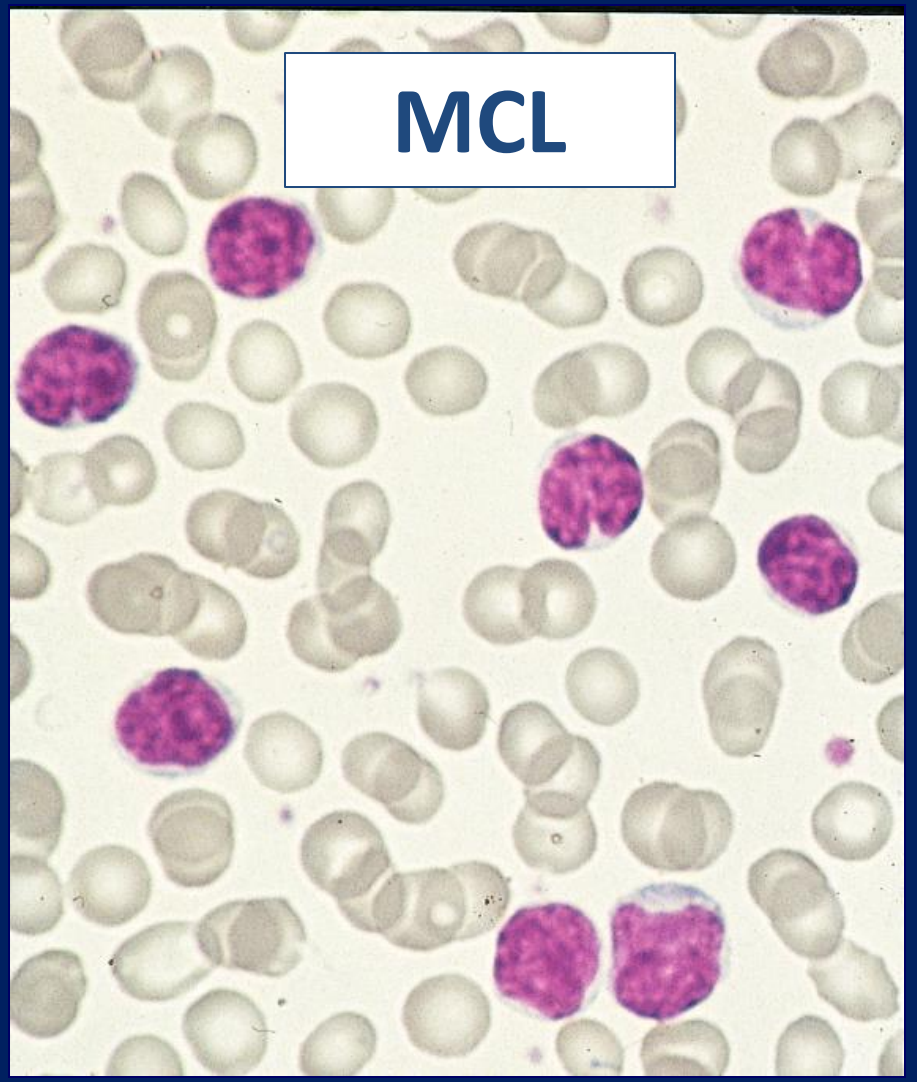

normaal

CLL *vs* MCL





Chronische lymfatische leukemie (CLL) / Kleincellig lymfocytair lymfoom (SLL)

Bloed

Leukocyten hoog aantal met monotone lymfocytose
Monoklonale B-lymfocyten >5 x 10^9/l
kleine cellen (6-10 µm), smalle cytoplasmazoom, zeer grof chromatine, kapotte cellen (Schollen, smudge cells)

Beenmerg cytologie

Vergelijkbare morfologie

Immunofenotype

CD19, zwak CD20, zwak smIg, **CD5**, CD23 (sterk)

Mutaties

TP53, *NOTCH1*, *SF3B1*, *ATM*, *BIRC3*

Mantelcel lymfoom

Bloed

vaak leukocytose met monotone kleine tot middelgrote lymfocyten, smalle cytoplasmazoom, fijn tot grof chromatine, kern vaak een klief, soms ook blastair!

Beenmerg cytologie

hetzelfde als het bloed, vaak sterk geinfiltreerd

Immunofenotype

CD19, CD20, sterk smIg (alleen sIgM/IgD), **CD5**, *geen* CD23, cycline D1

2 subtypen

- Klassiek (LNN): ongemuteerd IGHV, SOX11+
- *Leukemic non-nodal* (PB, BM, milt): gemuteerd IGHV, SOX11-

CLL *vs* MCL

Markers	chronische B-cel leukemieën				leukemisch B-NHL		
	B-CLL	B-PLL	HCL	HCLv	SLVL	MCL	FCL
SmIg-expressie	++^{w}	++^{s}	++	++	++	++	++
CyIg-expressie	±	±	-	-	±	-	-
IgH-isotype	μ,μδ,δ	μ,μδ	μ,μδ,γ,α	γ	μ,μδ,γ	μ,μδ	μ,μδ,γ
CD19	++	++	++	++	++	++^{w}	++
CD20	++^{w}	++	++^{s}	++	++	++^{s}	++
CD21	+	±	±	—	±	±	±
CD22	+^{w}	++^{s}	++^{s}	++	++^{s}	+	++
CD23	++	—	—	±	±	—	±
(CD24)	++	++	±^{p}	—	++	++	++
cyCD79	++	++	++	++	++	++	++
CD5	++	±	—	—	±	++	±
CD10	—	±	±	—	±	—	+^{w}
CD11c	+	—	++	+	+	—	—
CD25	±	—	++	—	±	—	—
CD103	—	—	++	+	±	—	—
(FMC7)	±	++^{s}	++	++	++	+	++
CD138	-	-	-	-	-	-	-

CLL *vs* MCL

Karakteristiek monotone lymfatische cellen immunofenotype:

pan-B cel

CD5-positief

Klassieke CLL	***Mantelcel NHL***
CD23 positief	CD23 negatief
zwak sIg (IgM/IgD)	sterk sIg (IgM/IgD)
overleving vele (tientallen) jaren	overleving mediaan circa 5-7 jaar

Monoclonale B cel lymfocytose (MBL)

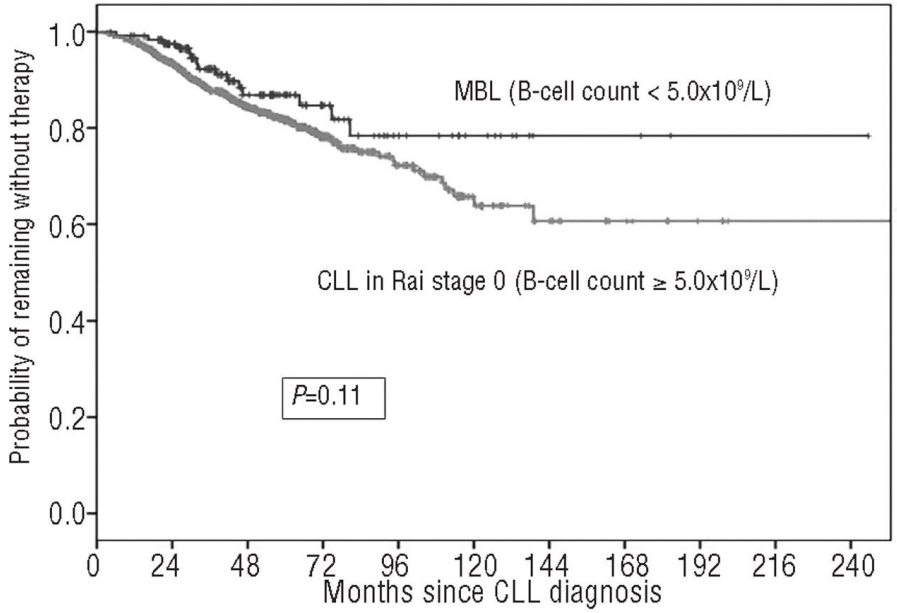
CLL vereist > 5 x 10^9/l $CD5^+$ monoclonale B cellen

Als dit er minder zijn:

- leukemisch lymfocytair lymfoom (SLL)
- Monoclonale B cel Lymfocytose (MBL)

MBL = “MGUS van de CLL”

- ’low-count’ <0.5 x 10^9/l
- ‘high-count’ 0.5-5 x 10^9/l



Rawstron. *N Engl J Med* 2008;359:575-83.

Molica. *Haematologica* 2011;96:277-83.

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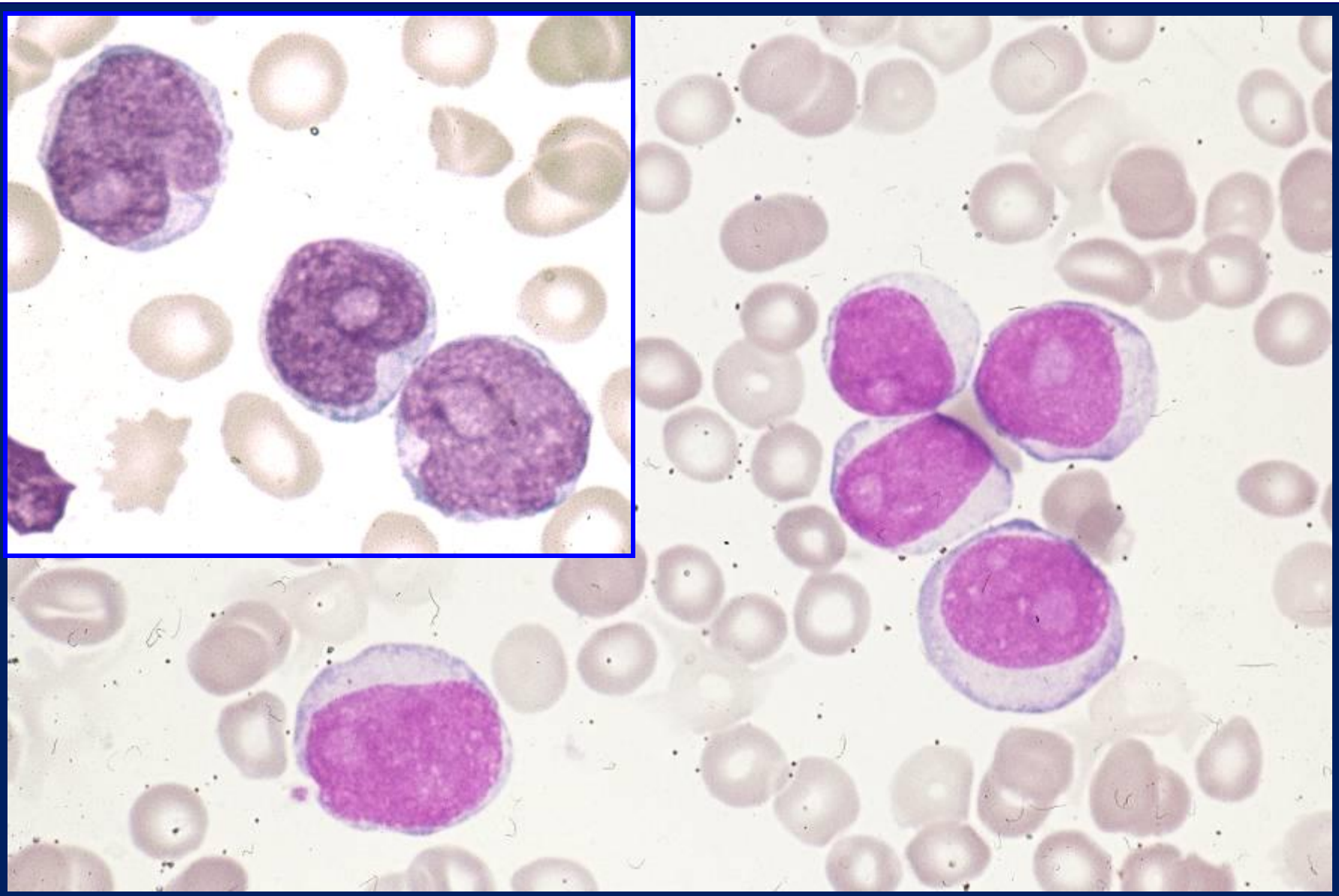

B-prolymphocytic leukemia (B-PLL)

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Bloed

Leukocyten hoog met >55% prolymfocyten

Aspect: grote cellen, ruim cytoplasma, ronde centrale celkern, prominente nucleolus.

Beenmerg cytologie

Idem als bloed, vaak sterke infiltratie

Immunofenotype

80% pan B: CD19, CD20, sterke smIg

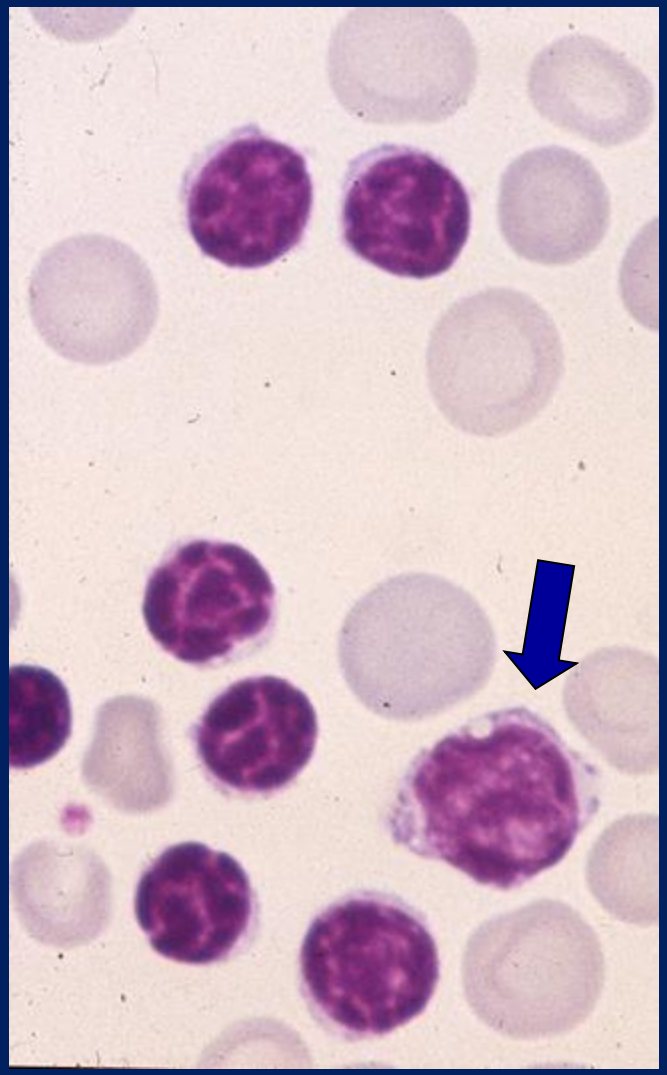
DD

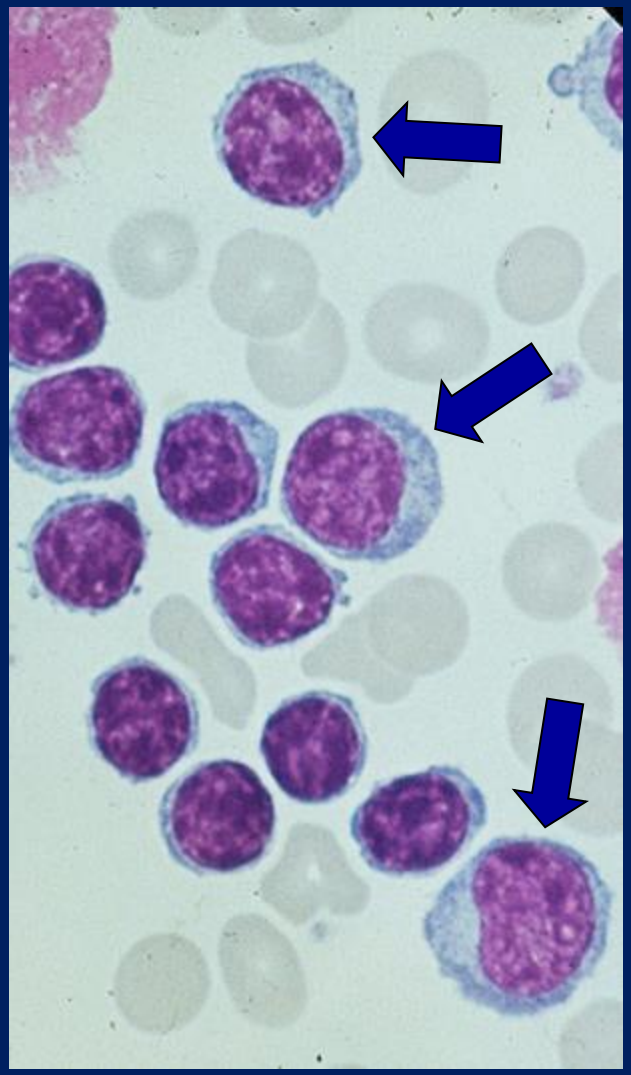
CLL in transformatie

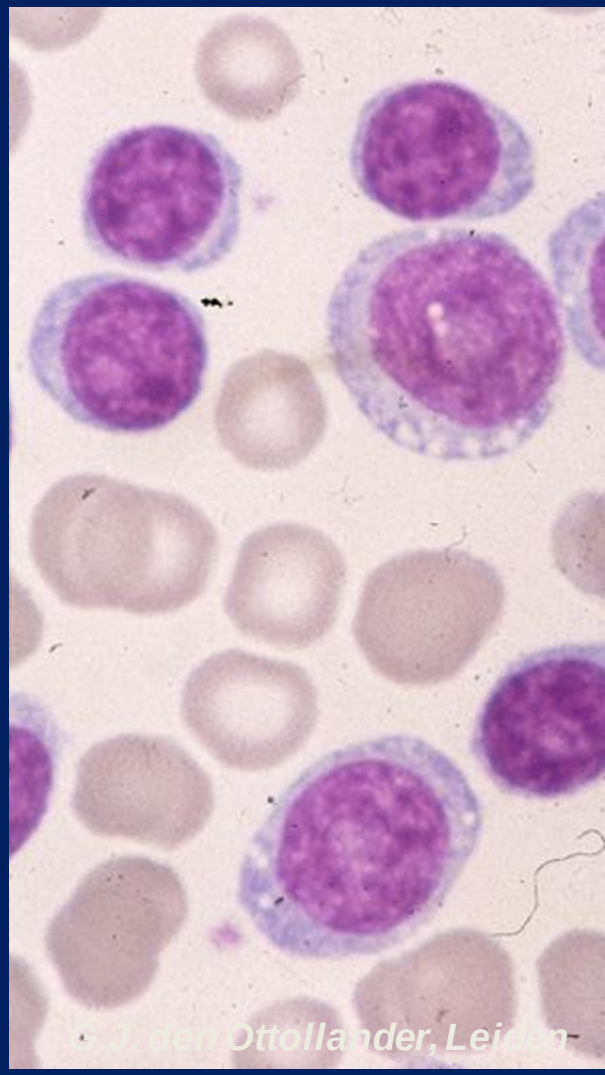
Milt B-cel lymfoom/leukemie met prominente nucleoli

leukemisch mantelcel lymfoom (met t[11;14])

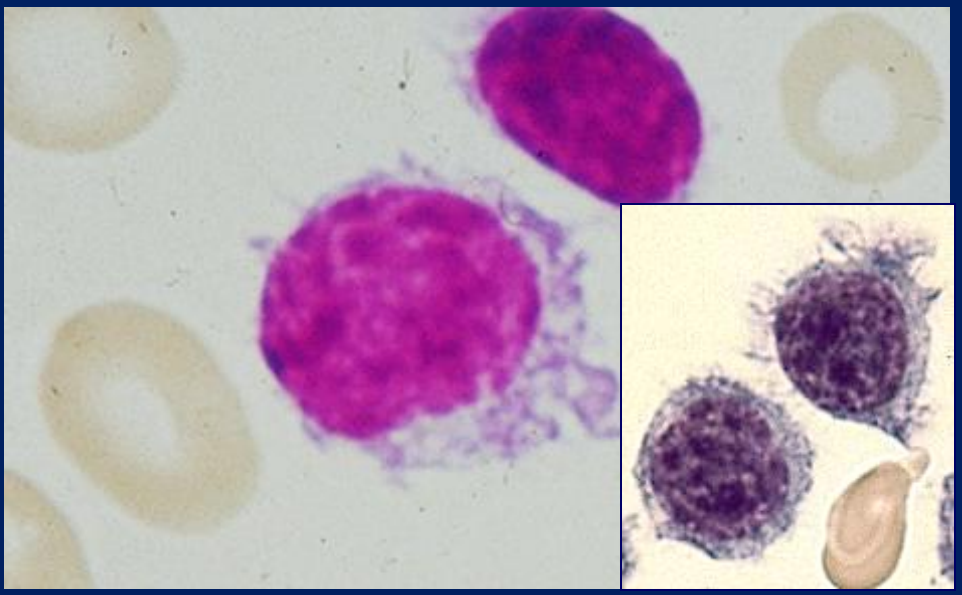
CLL *vs* CLL-PL *vs* PLL

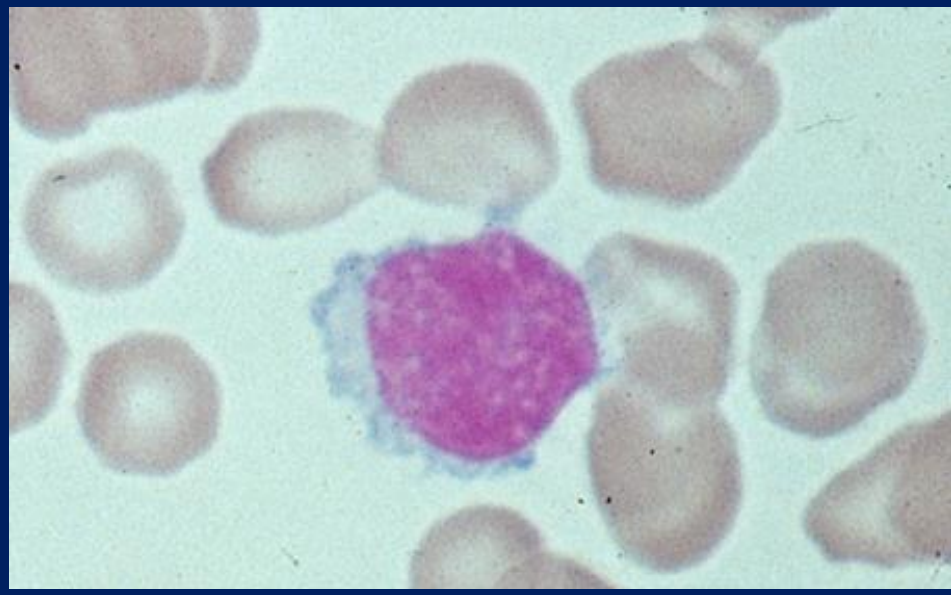


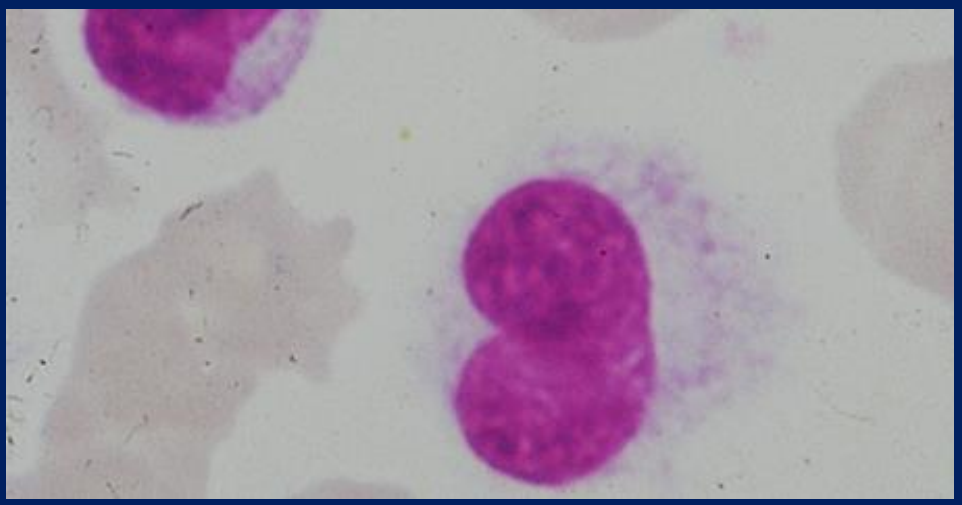


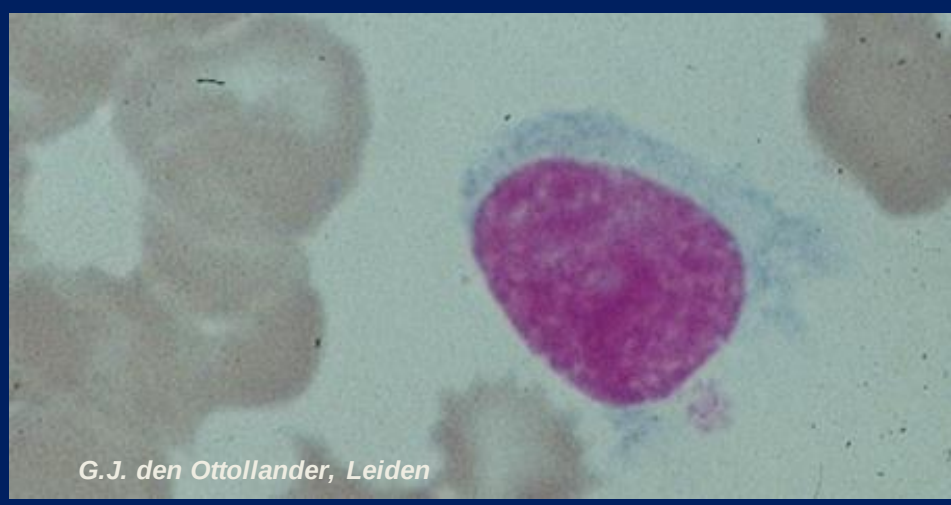


Morfologische uitdaging: differentiatie van HCL, HCL variant, LPL, SMZL









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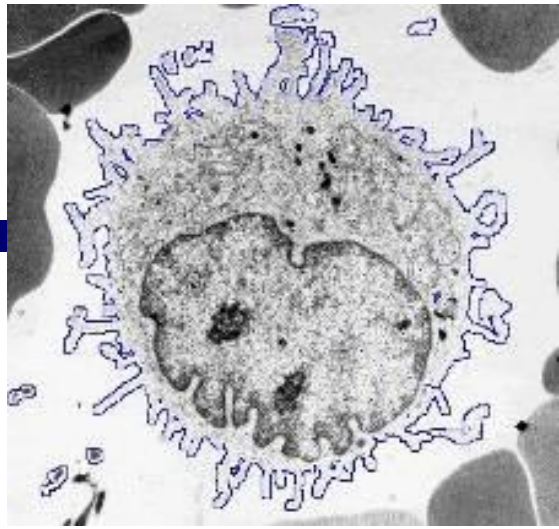
Hairy cell leukemie



Bloed

cytopenie, m.n. monocytopenie

zeldzaam: circulerende hairy cells.

Beenmerg cytologie

vaak ‘dry tap’

altijd biopsie verkrijgen

aspect: grote lymfoide cellen met ovale kern, fijn chromatine, vaal, ruim cytoplasma met harige uitlopers.

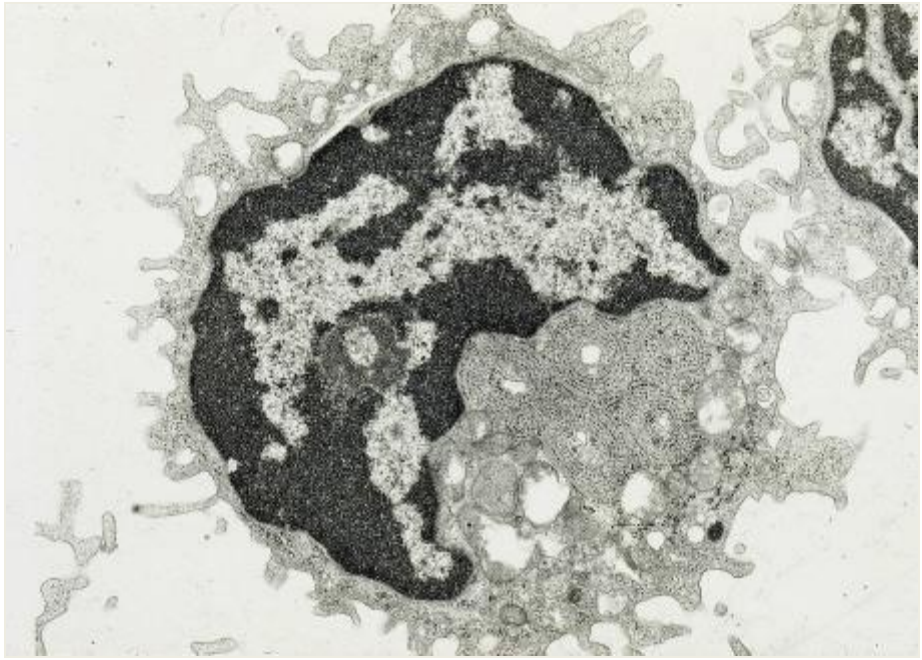
Immunofenotype

pan B (CD19, CD20, sterk sIg), CD25, CD11c, **CD103**

Genetica

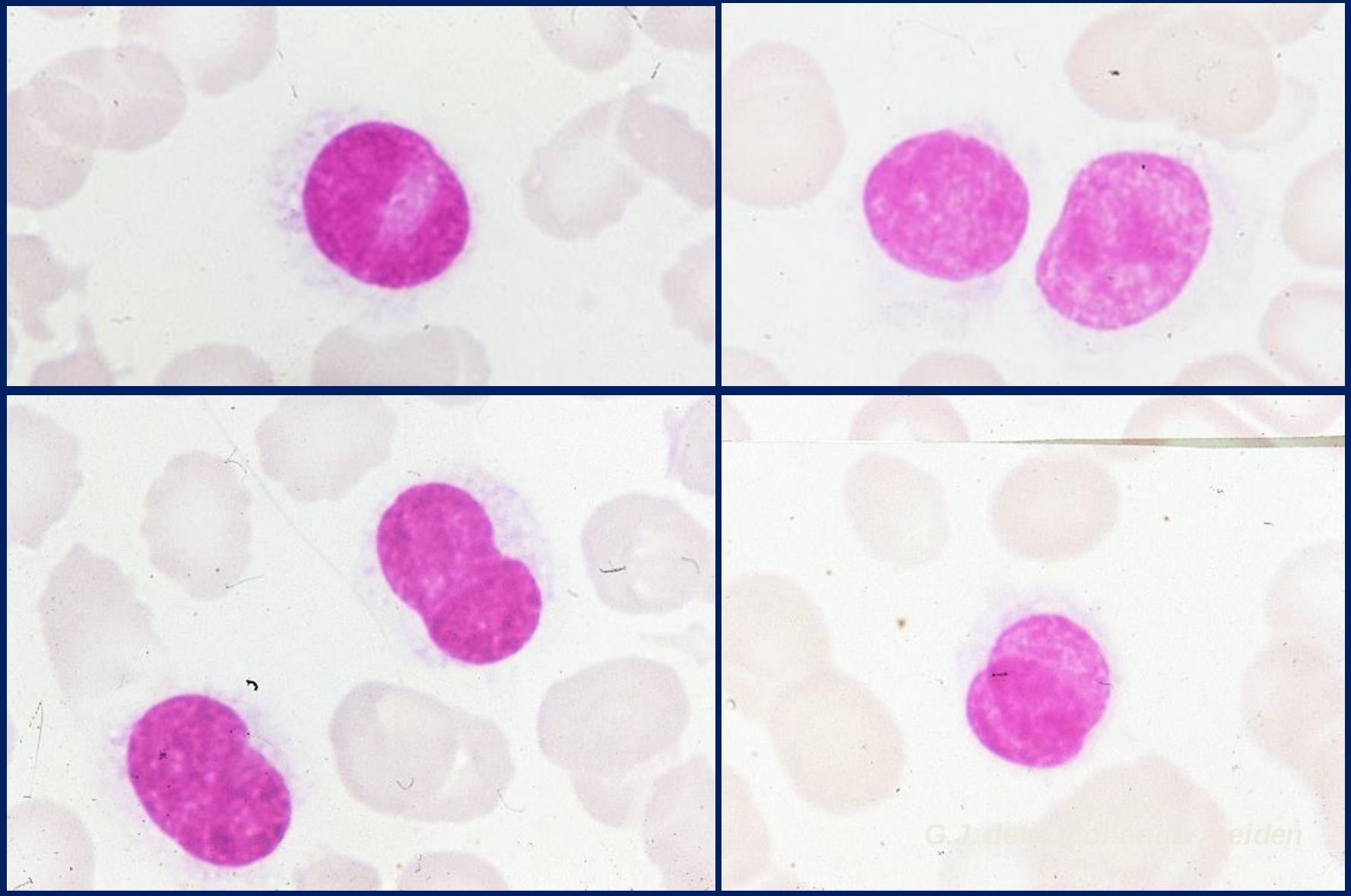
BRAF V600E mutation

Hairy cell morfologie



Dr. P. Brederoo, Dept. EM, Leiden University

Hairy cell morfologie



Immunofenotype van HCL

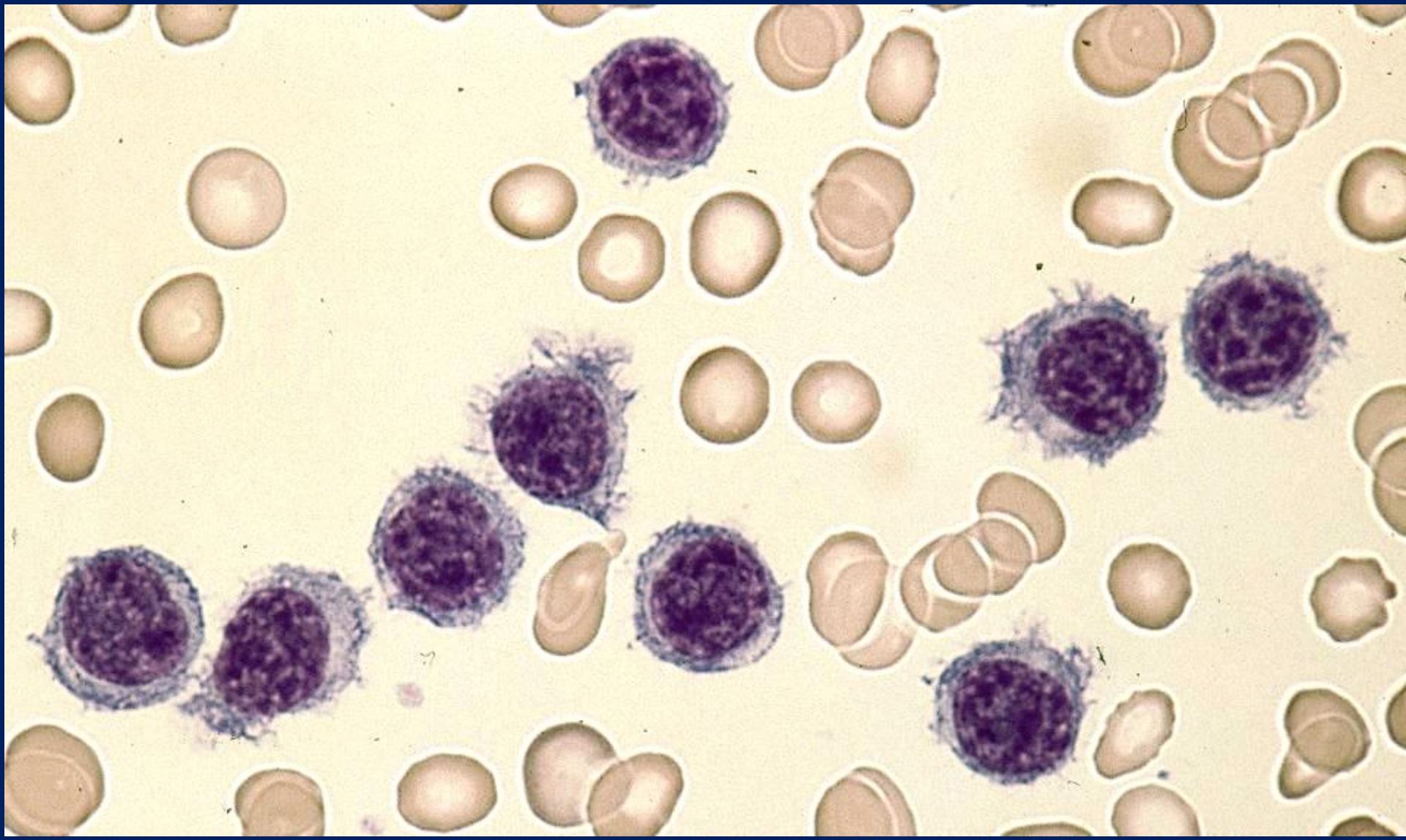
Markers	chronische B-cel leukemieën				leukemisch B-NHL		
	B-CLL	B-PLL	HCL	HCLv	SLVL	MCL	FCL
SmIg-expressie	$++^{w}$	$++^{s}$	++	++	++	++	++
CyIg-expressie	±	±	-	-	±	-	-
IgH-isotype	μ,μδ,δ	μ,μδ	μ,μδ,γ,α	γ	μ,μδ,γ	μ,μδ	μ,μδ,γ
CD19	++	++	++	++	++	$++^{w}$	++
CD20	$++^{w}$	++	$++^{s}$	++	++	$++^{s}$	++
CD21	+	±	±	—	±	±	±
CD22	$+^{w}$	$++^{s}$	$++^{s}$	++	$++^{s}$	+	++
CD23	++	—	—	±	±	—	±
(CD24)	++	++	$\pm^{p}$	—	++	++	++
cyCD79	++	++	++	++	++	++	++
CD5	++	±	—	—	±	++	±
CD10	—	±	±	—	±	—	$+^{w}$
CD11c	+	—	++	+	+	—	—
CD25	±	—	++	—	±	—	—
CD103	—	—	++	+	±	—	—
(FMC7)	±	$++^{s}$	++	++	++	+	++
CD138	-	-	-	-	-	-	-

HCL *vs* HCLv (milt B-cel lymfoom/leukemie met prominente nucleoli)

umcg

Markers	chronische B-cel leukemieën				leukemisch B-NHL		
	B-CLL	B-PLL	HCL	HCLv	SLVL	MCL	FCL
SmIg-expressie	$++^{w}$	$++^{s}$	++	++	++	++	++
CyIg-expressie	±	±	-	-	±	-	-
IgH-isotype	μ,μδ,δ	μ,μδ	μ,μδ,γ,α	γ	μ,μδ,γ	μ,μδ	μ,μδ,γ
CD19	++	++	++	++	++	$++^{w}$	++
CD20	$++^{w}$	++	$++^{s}$	++	++	$++^{s}$	++
CD21	+	±	±	—	±	±	±
CD22	$+^{w}$	$++^{s}$	$++^{s}$	++	$++^{s}$	+	++
CD23	++	—	—	±	±	—	±
(CD24)	++	++	$\pm^{p}$	—	++	++	++
cyCD79	++	++	++	++	++	++	++
CD5	++	±	—	—	±	++	±
CD10	—	±	±	—	±	—	$+^{w}$
CD11c	+	—	++	+	+	—	—
CD25	±	—	++	—	±	—	—
CD103	—	—	++	+	±	—	—
(FMC7)	±	$++^{s}$	++	++	++	+	++
CD138	-	-	-	-	-	-	-

Milt marginale zone lymfoom (SLZL)



Splenic lymphoma with villous lymphocytes
WHO: splenic marginal zone lymphoma

Bloed

Middelgrote lymfocyten met karakteristieke villi

Beenmerg cytologie

Idem. als bloed.

Immunofenotype

pan B: CD19, CD20, sterke smIg (IgM/IgD),
geen CD5, *geen* CD10, *geen* cyclin D1, *geen* CD103

DD:

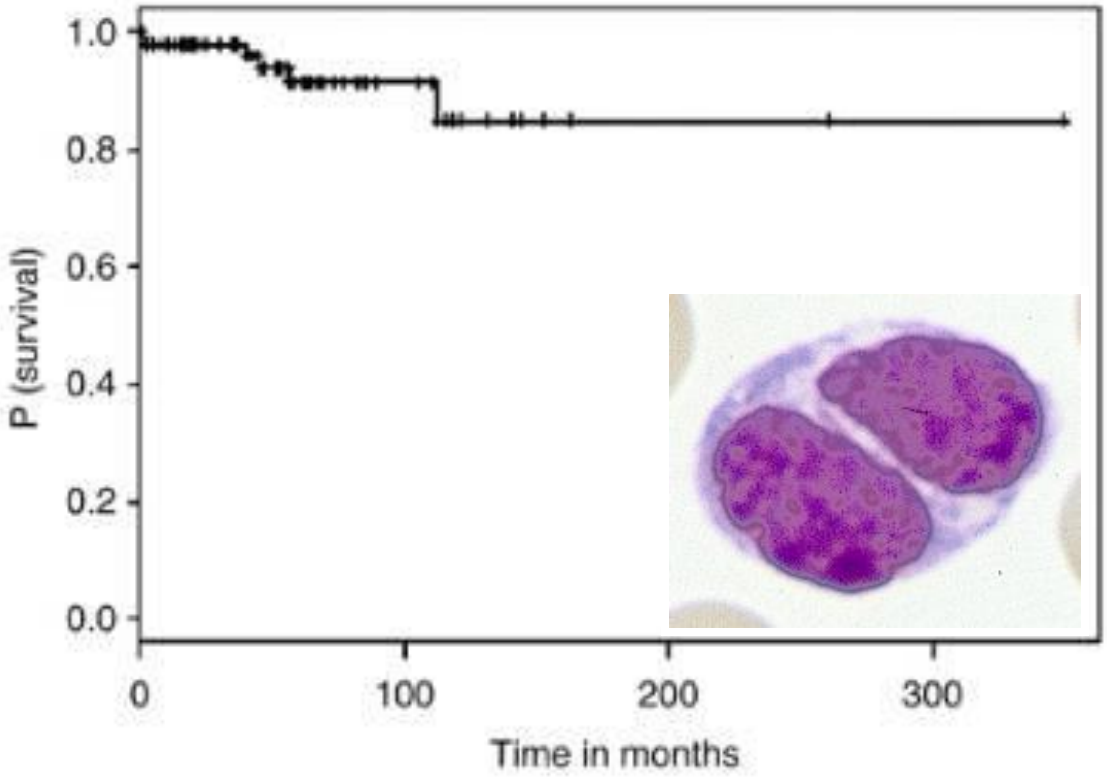
CLL, HCL, leukemisch rijpe B-NHL

??

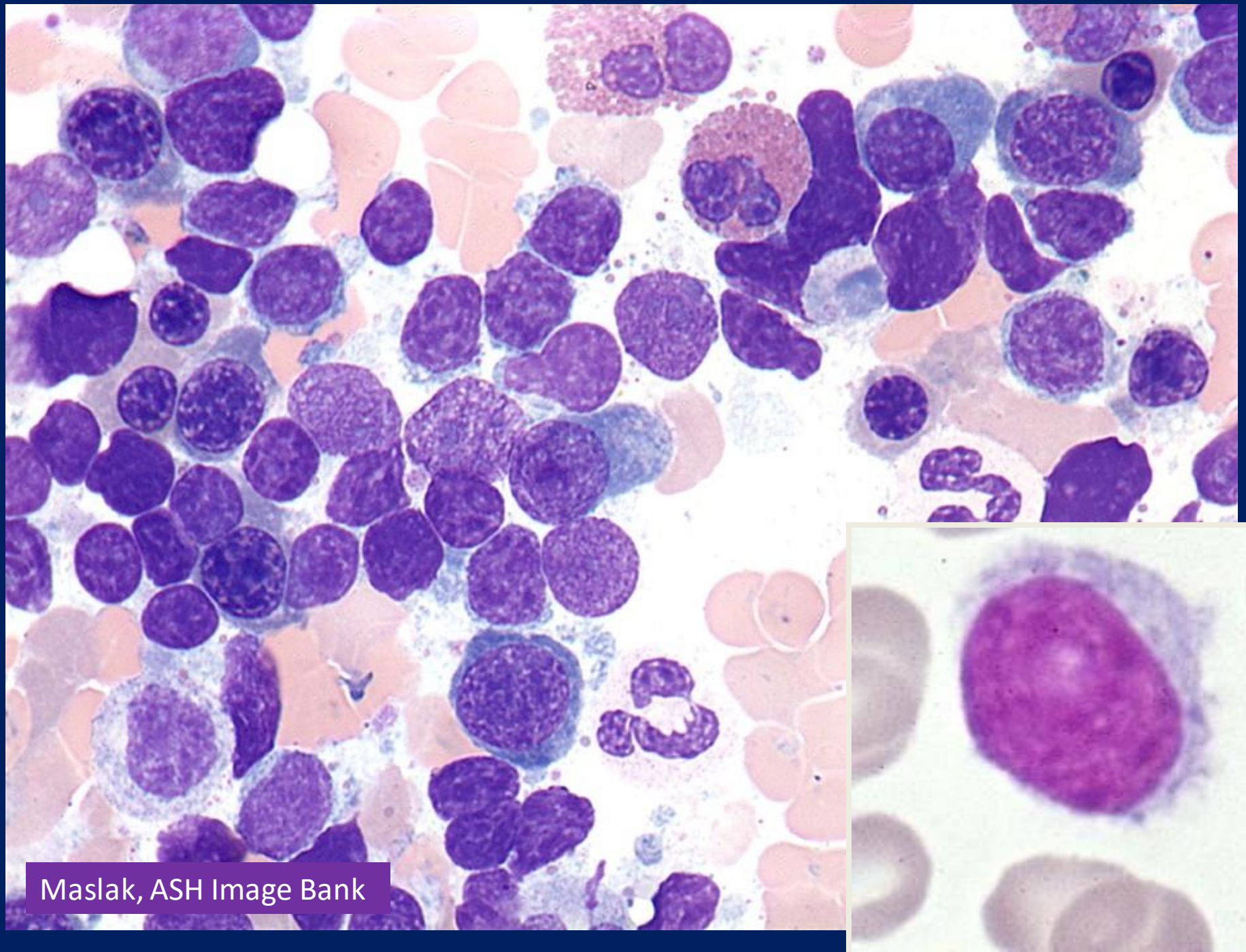
(Persistent) polyclonal B-cell lymphocytosis with binucleated lymphocytes

N = 111, 82% vrouw, leeftijd: mediaan 40 (19-66), roken: 98%

Splenomegalie: 10%



Cornet. *Leukemia* 2009;23:419-22



Maslak, ASH Image Bank

Lymfoplasmacytair lymfoom (M. Waldenström)

Bloed

vaak normaal, of cytopeen, of circulerende lymfoide cellen.
Agglutinatie van erytrocyten, M-proteine.

Beenmerg cytologie

Vaak grote aggregraten van lymfoide cellen in mengsel van CLL-achtige cellen, plasma cellen, mestcellen en cellen met plasmacytoide differentiatie.

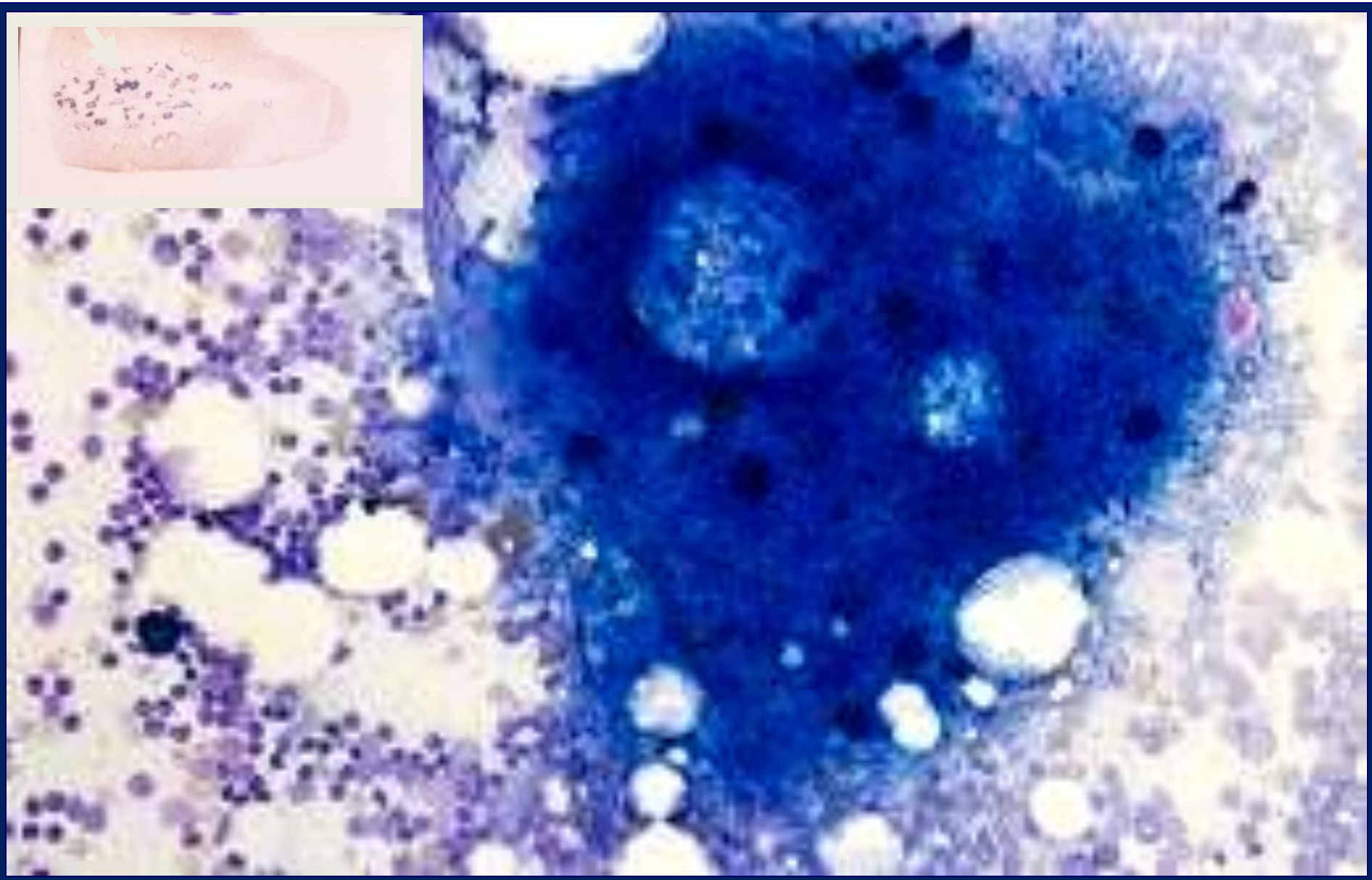
Immunofenotype

pan B: CD19, CD20, sterke smIg, deels cyIg

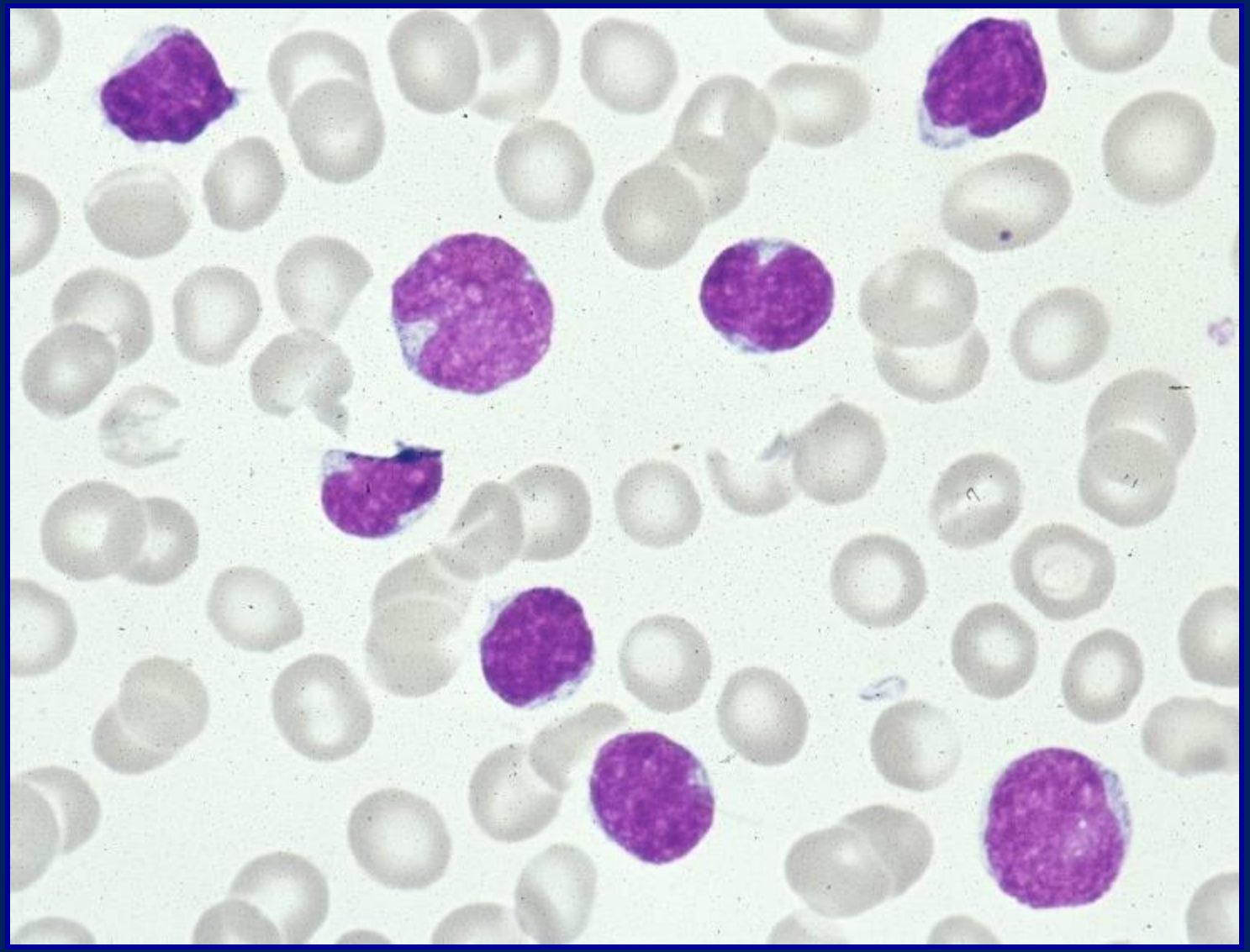
Genetica

MYD88 L265P mutatie

Lymfoplasmacytair lymfoom (M. Waldenström)



Leukemisch folliculair lymfoom



Folliculair lymfoom

Bloed

meestal normaal leukocytengetal, soms wisselend percentage afwijkende lymfocyten, met gekliefde kern, wandstandige nucleoli

Beenmerg cytologie

vaak normaal, terwijl het BIOPT dan positief is, tgv paratrabeculaire lokalisatie

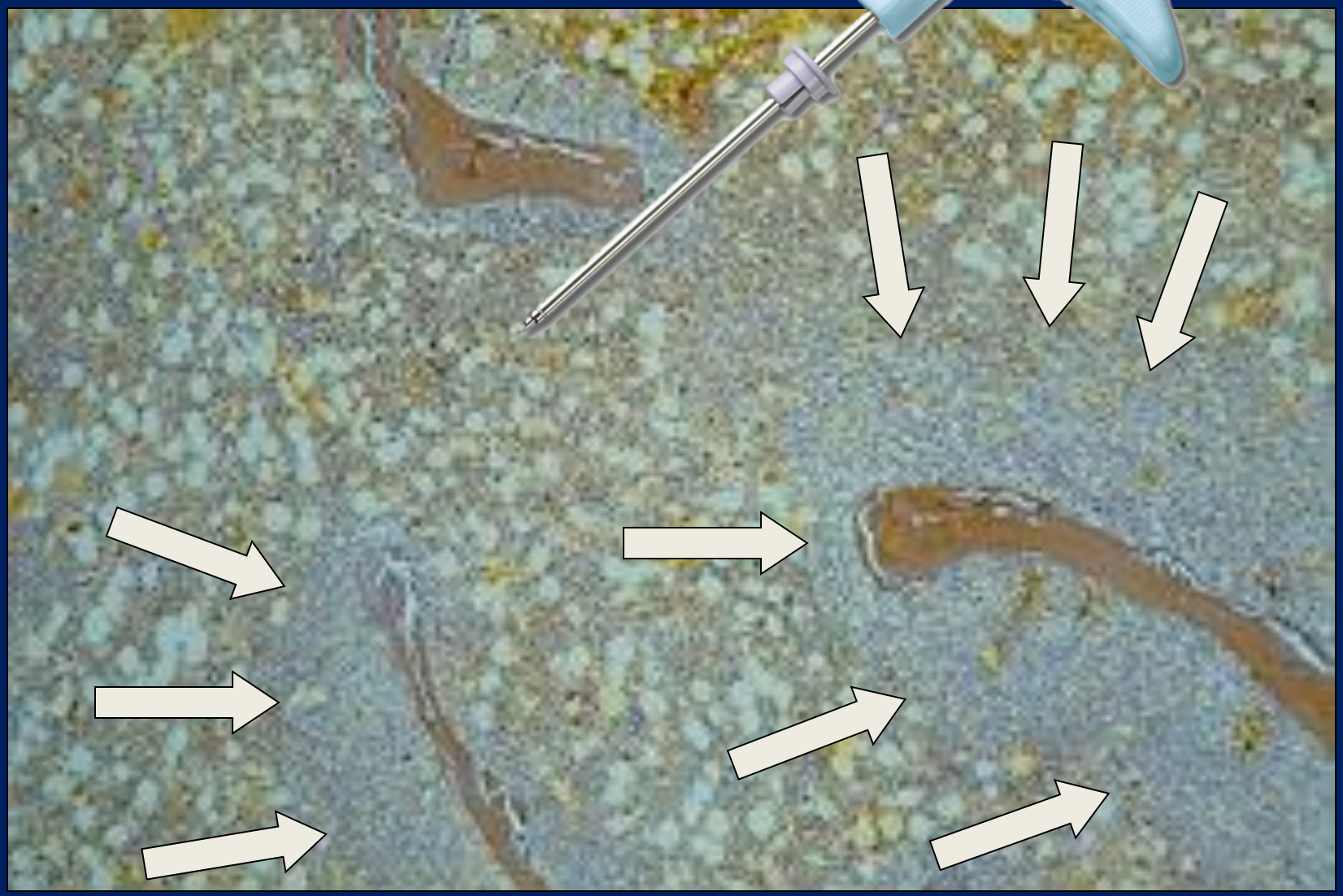
Immunofenotype

pan B: CD19, CD20, sterk smIg, CD10 (zwak)

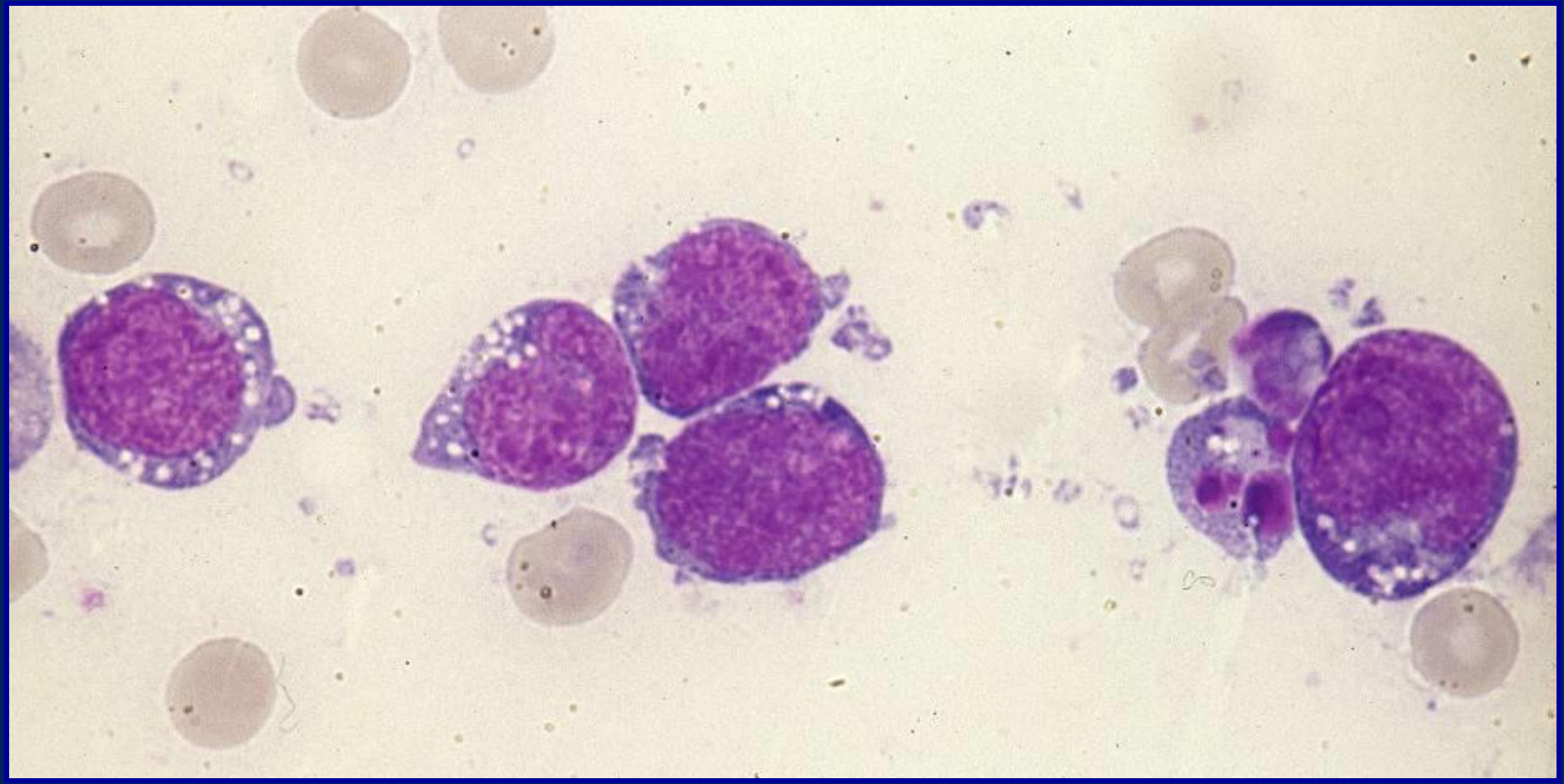
DD

reactieve lymfocytose, andere NHL's

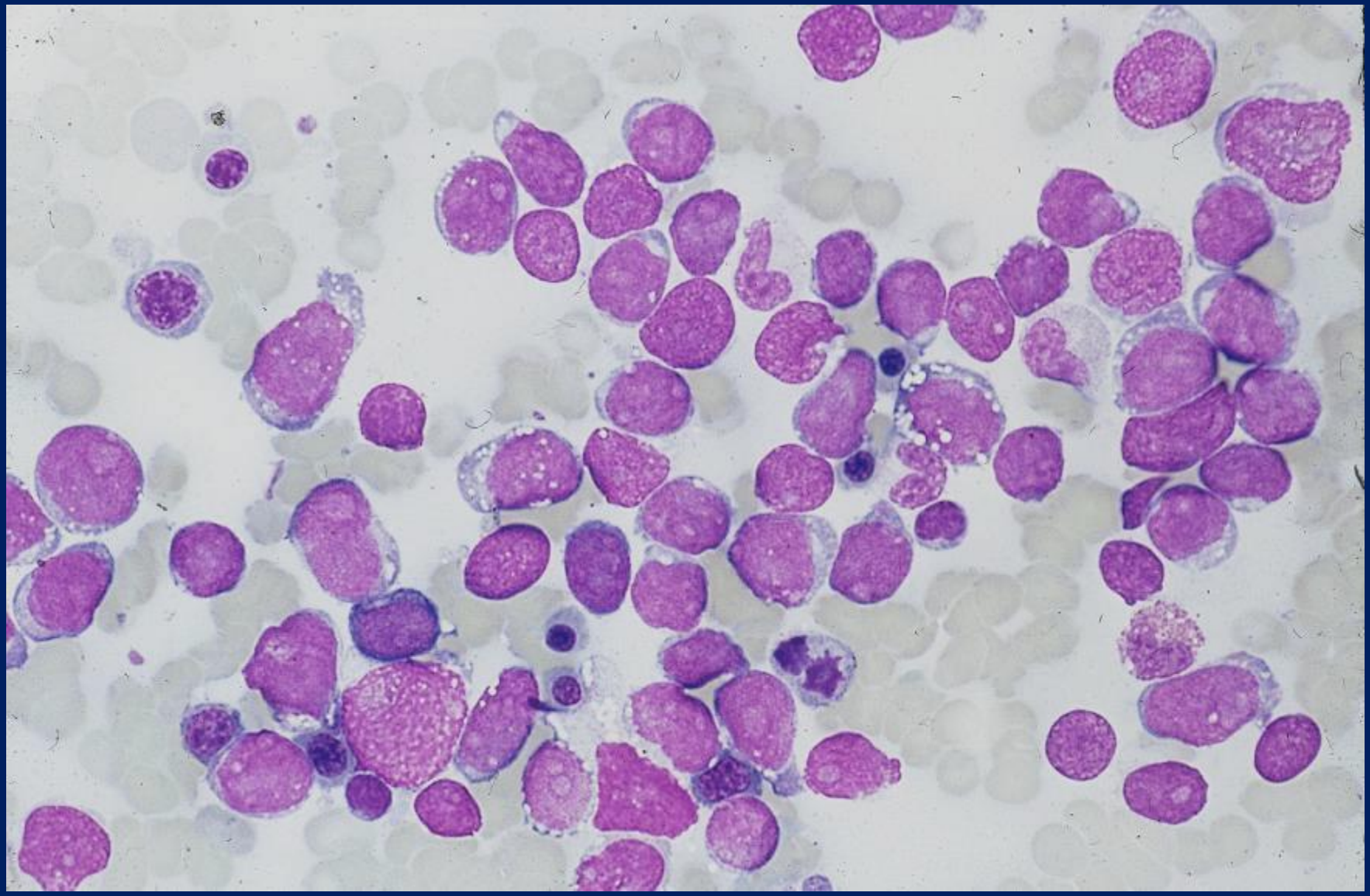
Aspiraat is niet altijd representatief!



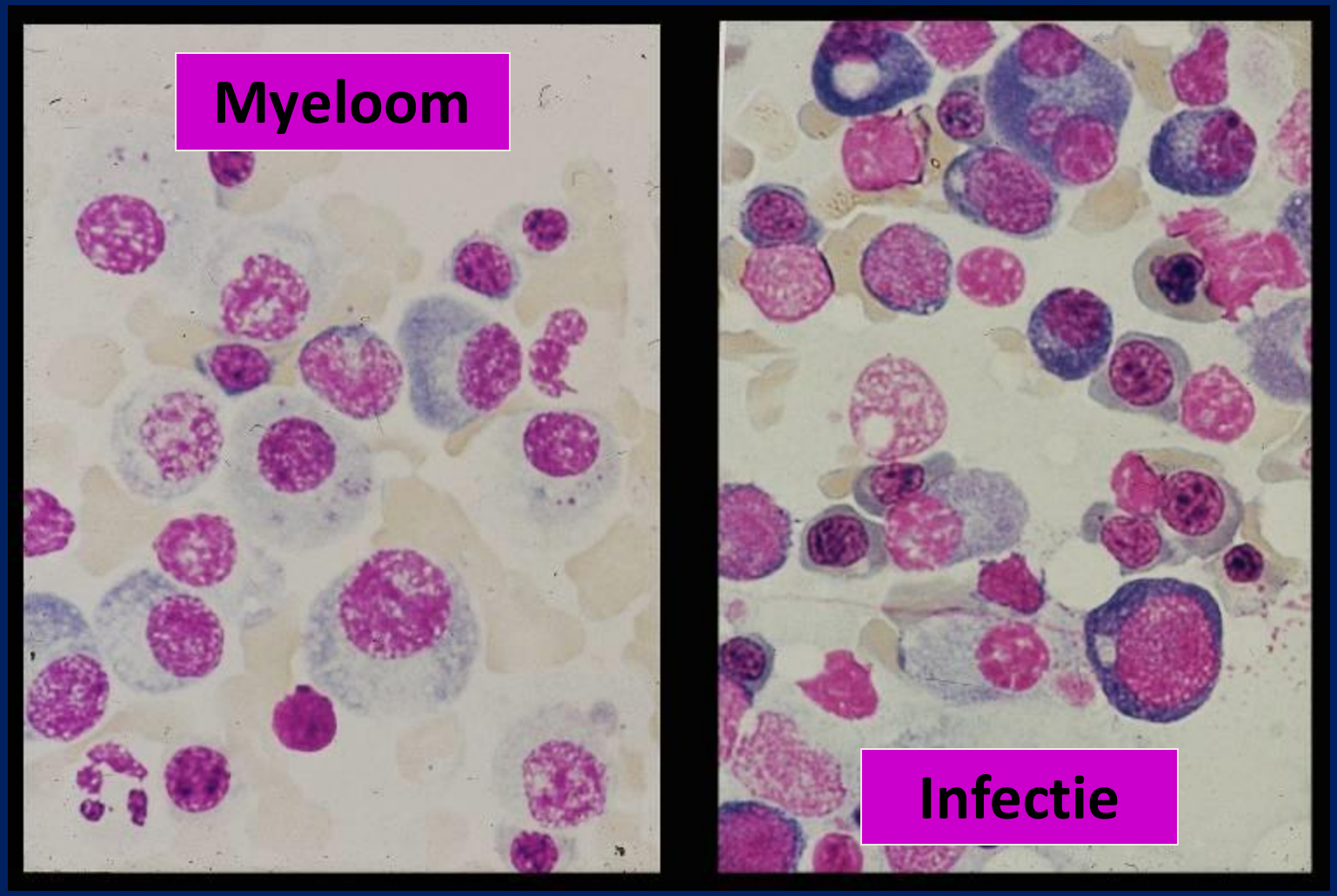
Burkitt lymfoom/leukemie



BM met DLBCL infiltratie



Een toename van plasmacellen…

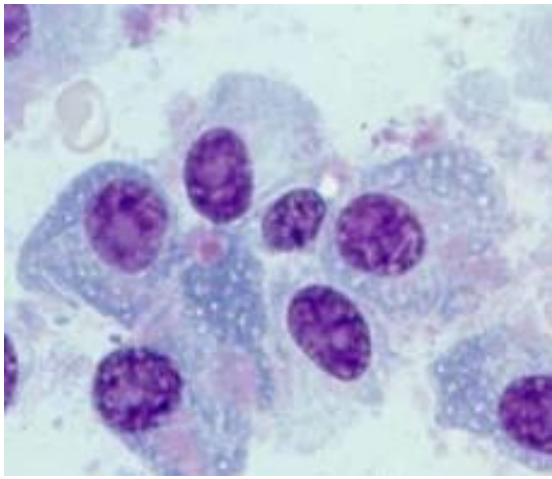


Criteria Multipel Myeloom (2014)

	M-protein	BM plasma cells
MGUS (non-IgM, IgM, light chain)	<30 g/l	<10%
Smouldering myeloma	>30 g/l	10-60%
Multiple myeloma	(+)	>10%

"myeloma defining events" -
- CRAB
- clonal plasma cells in BM >60%
- FLC ratio (involved:uninvolved)
- >1 focal lesions on MRI

Solitary plasmacytoma (w/ minimal marrow involvement)
POEMS syndrome
Systemic AL amyloidosis



Rajkumar. *Lancet Oncol* 2014;15:e538-48

Multipel myeloom (M. Kahler)

Bloed

vaak normaal of cytopenie;
agglutinatie van de erytrocyten

Beenmerg cytologie

>10% plasma cellen (myeloom cellen)
typische abnormaliteiten: pleiomorf,
centrale kern, groter (of juist kleiner), nucleoli,
Dutcher/Russell bodies, morula cellen, flame cellen

Immunofenotypering

expressie van CD38, CD138, CD56 en CD45dim

DD bij perifere lymfocytose

Figure 2		DIFFERENTIAL DIAGNOSIS		ANCILLARY TESTS
Small, round nuclei →				Flow cytometry CLL FISH panel FISH *CCND1/IGH*
Folded or cleaved nuclei →			T-cell lymphomas Pertussis*	Flow cytometry FISH *CCND1*/IGH, *BCL2* Tissue biopsy
Villous cytoplasm →			T-PLL LPL	Flow cytometry *BRAF*
Plasmacytoid →				Flow cytometry SPEP/UPEP *MYD88* L265P Myeloma FISH panel
Prominent nucleoli →				Flow cytometry Cytogenetics
Large cells →				Flow cytometry FISH *MYC* *CCND1/IGH* *ALK*

George, *Hematologist* 2015;12(6)

Take home messages

Histopathologie essentieel in het stellen van de meeste B-cel lymfomen.

Het grote merendeel van de B-cel lymfatische beelden vereist flowcytometrie, en soms (lees: steeds vaker) ook moleculair en cytogenetisch onderzoek.

Flowcytometrie alléén kan valkuilen opleveren.

Klinisch beeld en morfologie kunnen richting geven aan de DD.

Mature T/NK-cell neoplasms (2016 rev)

T-cell prolymphocytic leukemia

T-cell large granular lymphocytic leukemia

Chronic lymphoproliferative disorder of NK cells

Aggressive NK-cell leukemia

Systemic EBV1 T-cell lymphoma of childhood

Hydroa vacciniforme–like lymphoproliferative disorder

Adult T-cell leukemia/lymphoma

Extranodal NK-/T-cell lymphoma, nasal type

Enteropathy-associated T-cell lymphoma

Monomorphic epitheliotropic intestinal T-cell lymphoma

Indolent T-cell lymphoproliferative disorder of the GI tract

Hepatosplenic T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma

Mycosis fungoides

Sézary syndrome

Primary cutaneous CD301 T-cell lymphoproliferative disorders

Lymphomatoid papulosis

Primary cutaneous anaplastic large cell lymphoma

Primary cutaneous gamma-delta T-cell lymphoma

Primary cutaneous CD81 aggressive epidermotropic cytotoxic T-cell lymphoma

Primary cutaneous acral CD81 T-cell lymphoma

Primary cutaneous CD41 small/medium T-cell lymphoproliferative disorder

Peripheral T-cell lymphoma, NOS

Angioimmunoblastic T-cell lymphoma

Follicular T-cell lymphoma

Nodal peripheral T-cell lymphoma with TFH phenotype

Anaplastic large-cell lymphoma, ALK1

Anaplastic large-cell lymphoma, ALK2

Breast implant–associated anaplastic large-cell lymphoma

Swerdlow. *Blood* 2016;127:2375-90

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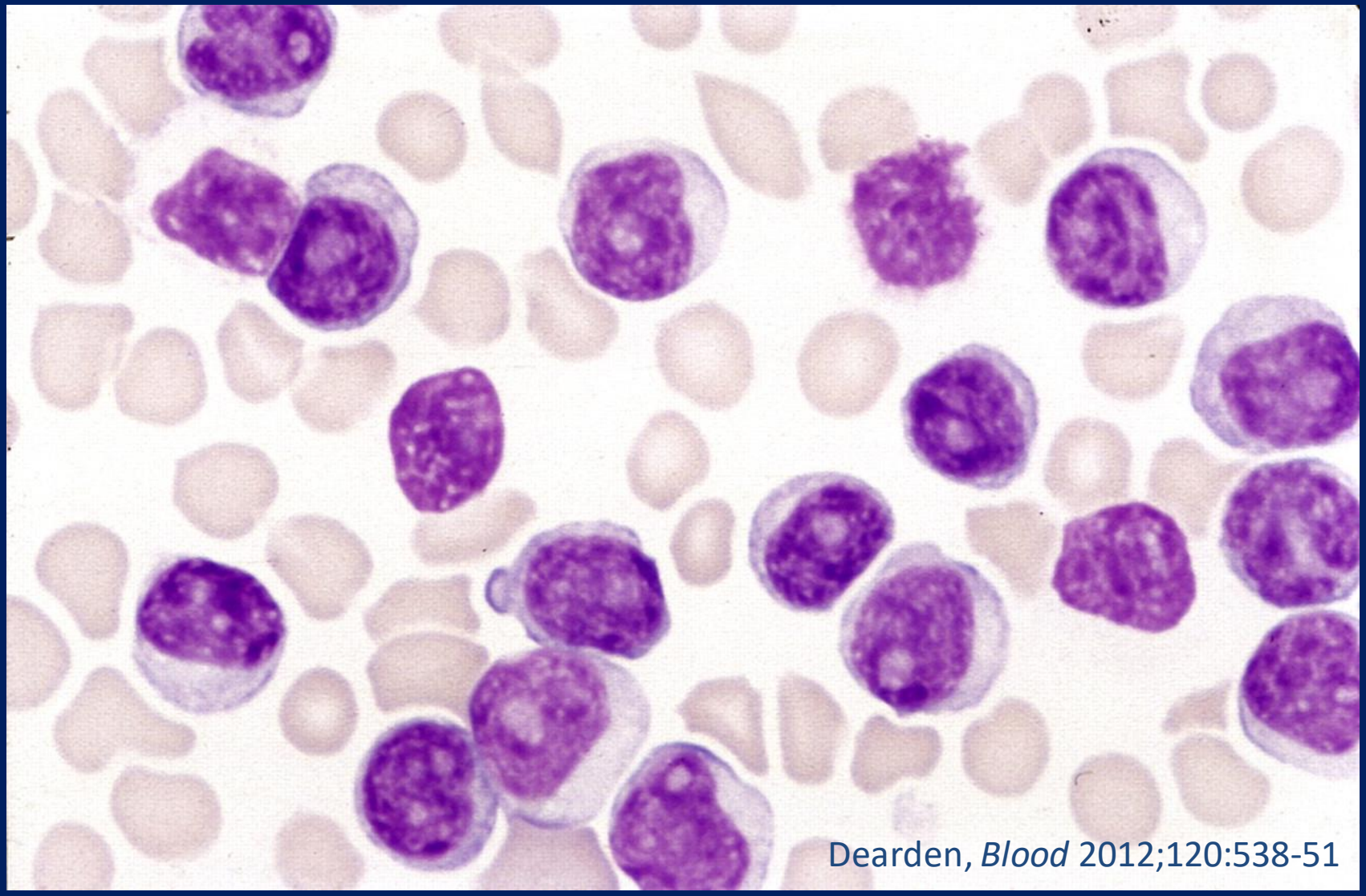
Dearden, *Blood* 2012;120:538-51

T-prolymphocytic leukemia (T-PLL)

umcg

Bloed

Vaak zeer hoog leukocytengetal (>100 x 10^e9/l)

Aspect: **grote** cellen, ruim cytoplasma, ronde centrale celkern, **prominente nucleolus**.

Beenmerg cytologie

Idem als bloed, vaak ook infiltratie LNN, huid, slijmvliezen

Immunofenotype

Meestal CD4, soms ook CD8; CD52 **pos**; TdT **neg**

Cytogenetica

Chromosoom 14 (TCR alfa/delta, TCL-1) afwijkingen

DD

T-ALL (TdT^+), T-LGL, ATLL

??

Jain & Prabhash, *Blood* 2010;115:1668

Adult T cell leukemia / lymphoma

Bloed

Opvallend gelobde kernen (“flower cells”)

Beenmerg cytologie

Idem als bloed, vaak ook infiltratie LNN, weefsels

Immunofenotype

Pos voor CD4, CD25 sterk; meestal ook CD30 **pos** en CD7 **neg**

Infectie

HTLV-1 virusinfectie

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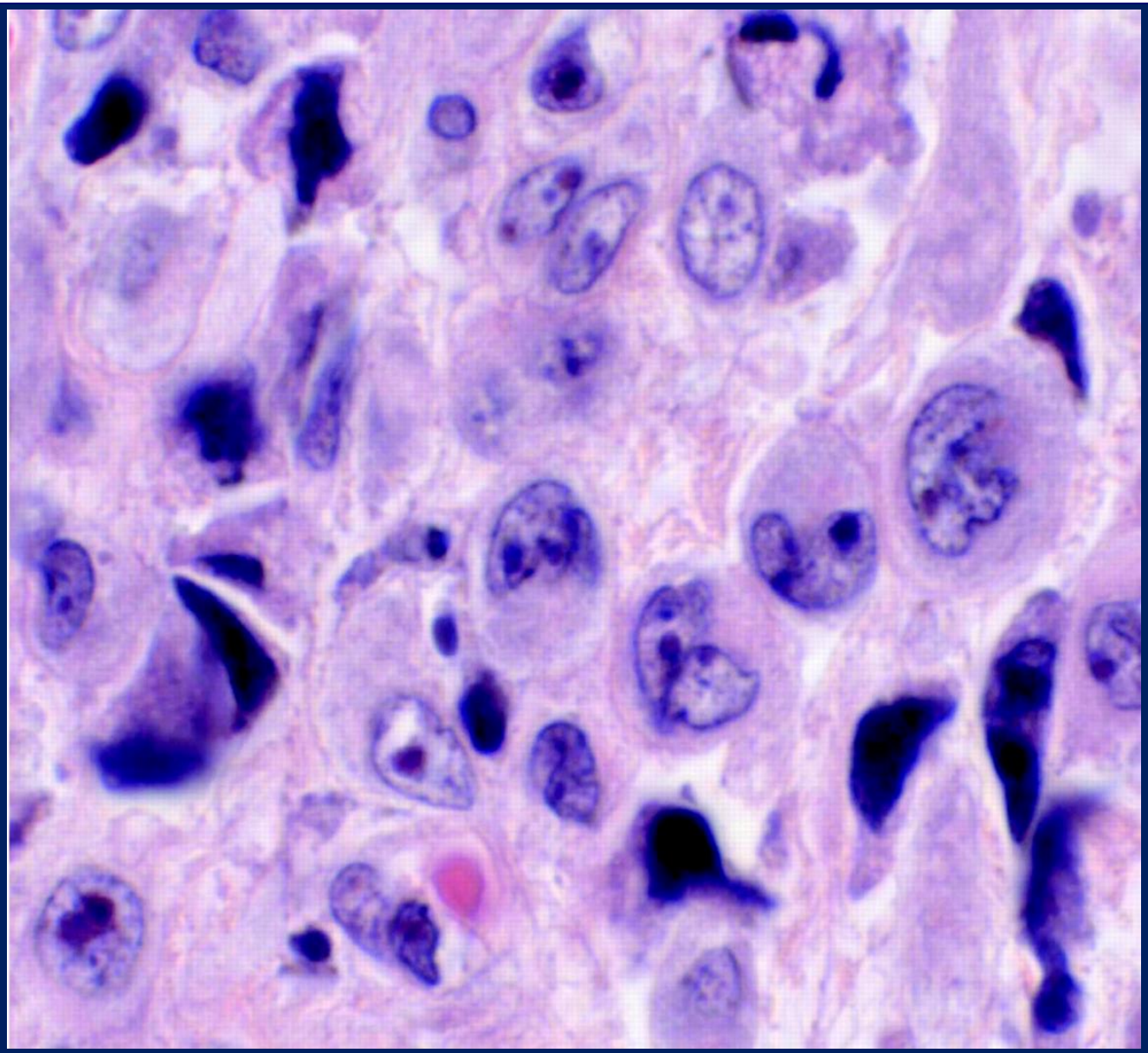

Anaplastisch large cell lymphoma (ALCL)

Bloed

Wisselende morfologie; meestal ‘hallmark cells’

Beenmerg cytologie

ALK-pos: soms beperkt aanwezig.

ALK-neg: zeldzaam.

Immunofenotype

Meestal CD4, soms ook CD8; TdT **neg**

Cytogenetica

ALK-pos: t(2;5)

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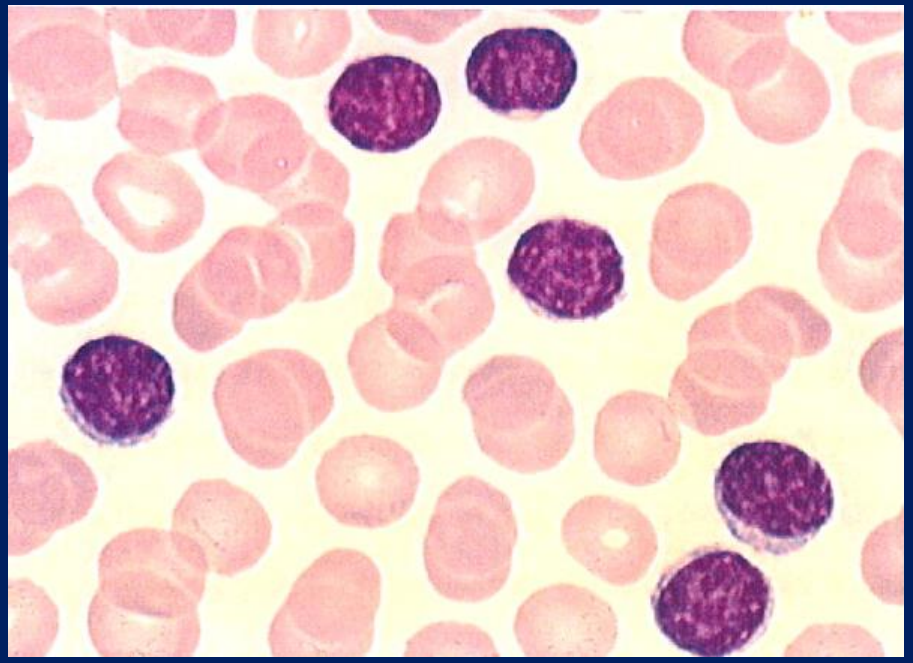

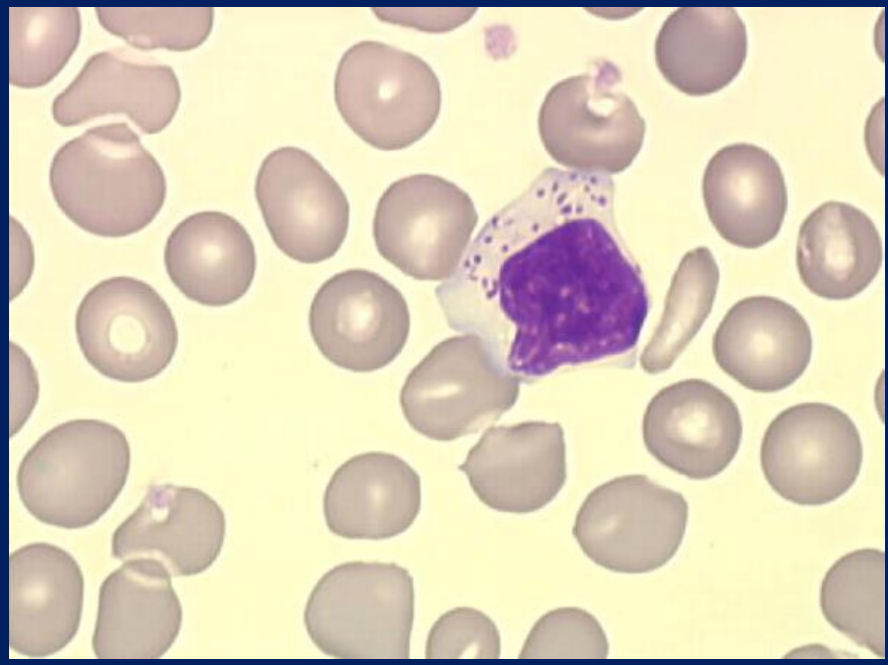

Lamy & Loughran. *Blood* 2011;117:2764-74

T-large granular lymphocytic leukemia

Bloed

Middelgrote / grote lymfatische cellen met ruim cytoplasma met azurofiele korrels.

Beenmerg cytologie

Soms beperkt.

Immunofenotype

T-cel: CD2+CD3+ $CD4^{-}CD8^{+}$ CD5/CD7 vaak **neg**

NK cel: $CD2^{+}CD3^{+}CD8^{+/-}$ $CD16^{+}$ CD56/CD57 soms

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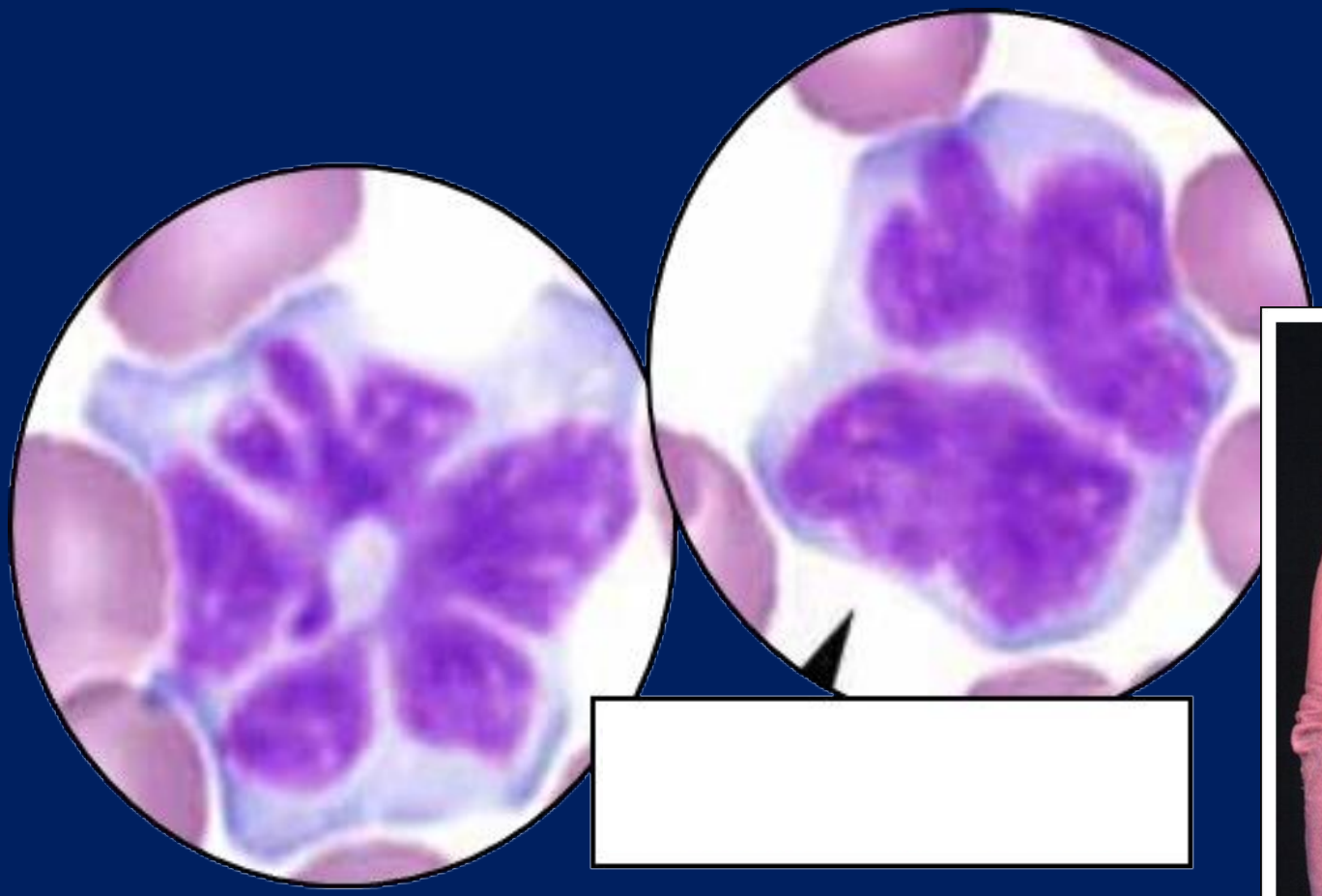

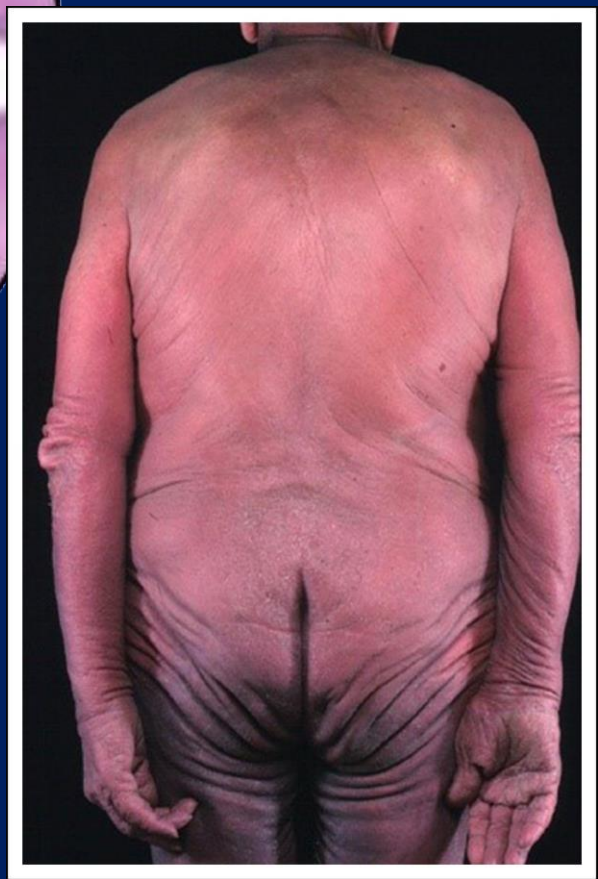

Sézary syndroom

T-cellymfoom van de huid

Laat stadium van mycosis fungoides / lymfadenopathie

Bloed / huid / (beenmerg)

Cerebriforme nuclei, soms met “scherpe” vouw

Immunofenotype

CD3, CD4+, meestal CD8 **neg**

Cytogenetica

Geen specifieke afwijkingen