GIORNATE EMATOLOGICHE VICENTINE

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Quali implicazioni cliniche della nuova classificazione WHO nelle malattie linfoproliferative?

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Disclosures of Alberto Zamò

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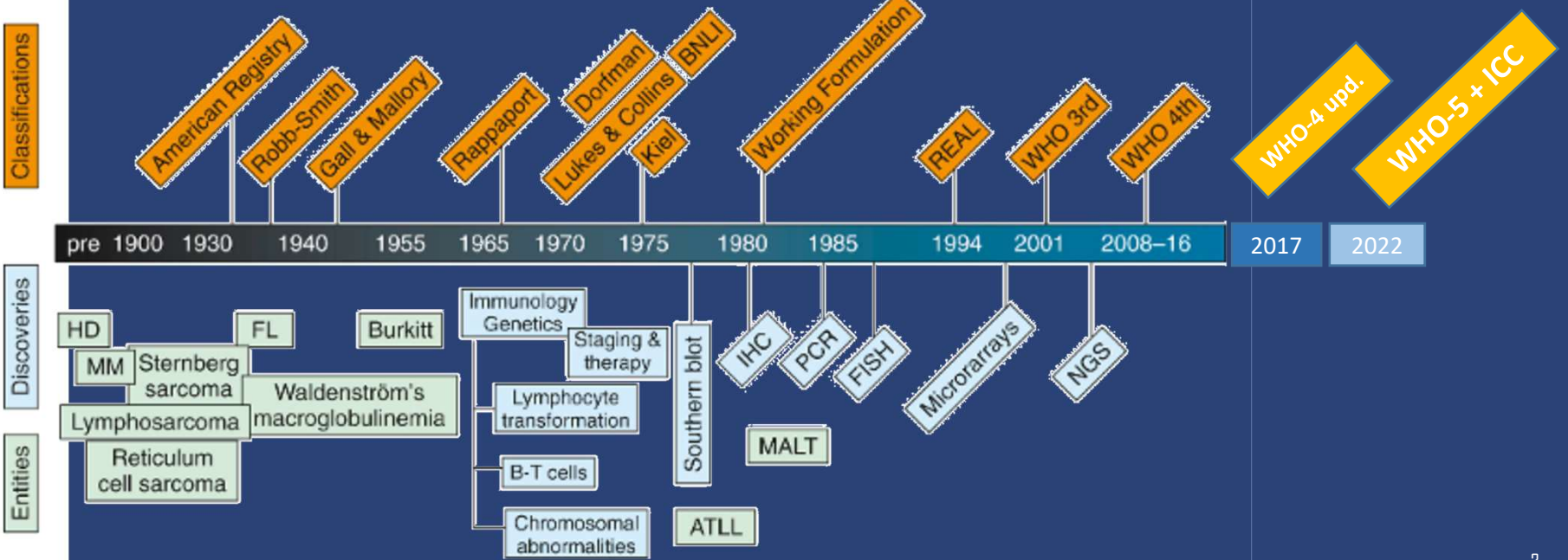
Evoluzione delle classificazioni dei linfomi



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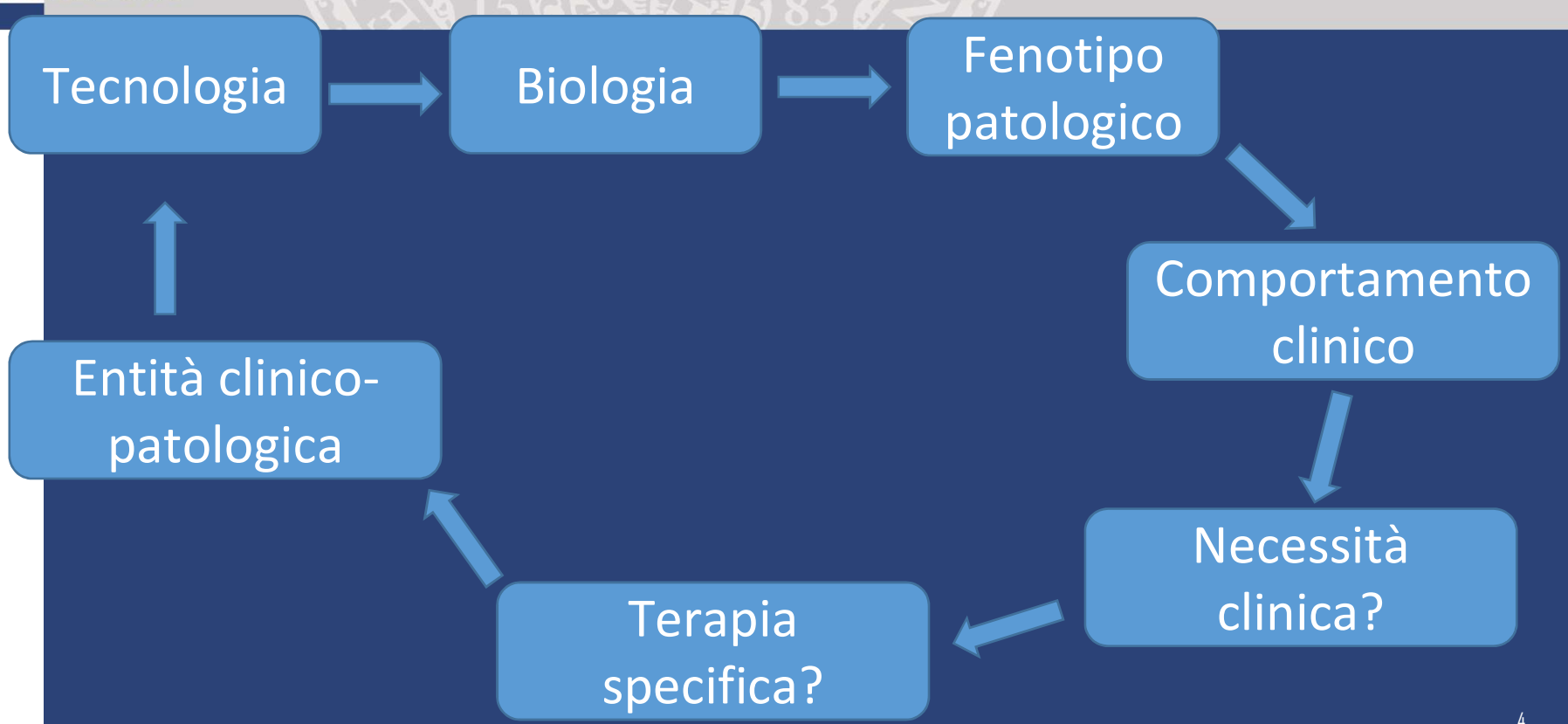

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The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

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Leukemia (2022) 36:1720–1748; https://doi.org/10.1038/s41375-022-01620-2

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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]

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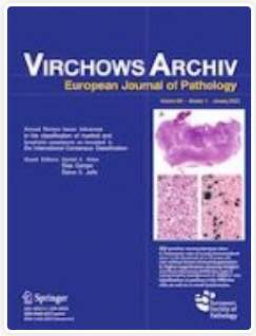

Volume 482, issue 1, January 2023

Annual Review Issue: Advances in the classification of myeloid and lymphoid neoplasms as revealed in the International Consensus Classification

Issue editors

Daniel A Arber, Elias Campo & Elaine S. Jaffe

20 articles in this issue

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WHO-5 vs ICC

- ICC più conservativa della WHO-5 (maggiore presenza di clinici)
- ICC pone più enfasi sulla genetica (più orientata al sistema USA/EU)

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Linfomi B

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WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Follicular lymphoma	Follicular lymphoma	Follicular lymphoma
- In situ follicular neoplasia	- In situ follicular B-cell neoplasm	- In situ follicular neoplasia
- Duodenal-type follicular lymphoma	- Duodenal-type follicular lymphoma	- Duodenal-type follicular lymphoma
Diffuse follicular lymphoma variant (not considered an entity)	FL with predominantly diffuse pattern (not considered an entity)	BCL2-R-negative, CD23-positive follicle center lymphoma (provisional entity)
Primary cutaneous follicle center lymphoma	Primary cutaneous follicle center lymphoma	Primary cutaneous follicle center lymphoma
Pediatric-type follicular lymphoma	Pediatric-type follicular lymphoma	Pediatric-type follicular lymphoma
Testicular follicular lymphoma	Not considered an entity	Testicular follicular lymphoma (distinct entity)
Large B-cell lymphoma with IRF4 rearrangement (provisional entity)	Large B-cell lymphoma with *IRF4* rearrangement (upgraded to distinct entity)	Large B-cell lymphoma with *IRF4* rearrangement (upgraded to a distinct entity)

Leukemia (2023) 37:18–34; https://doi.org/10.1038/s41375-022-01764-1

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WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Follicular lymphoma		Follicular lymphoma
- In situ follicular neoplasia		- In situ follicular neoplasia
- Duodenal-type follicular lympho		- Duodenal-type follicular lymphoma
Diffuse follicular lymphoma variant considered an entity)		BCL2-R-negative, CD23-positive follicle center lymphoma (provisional entity)
Primary cutaneous follicle center ly		Primary cutaneous follicle center lymphoma
Pediatric-type follicular lymphoma		Pediatric-type follicular lymphoma
Testicular follicular lymphoma		Testicular follicular lymphoma (distinct entity)

Follicular lymphoma (FL): from classic grading to biological grouping

The family of follicular lymphoma encompasses follicular lymphoma, in situ follicular B-cell neoplasm (ISFN), paediatric-type FL and duodenal-type FL. There are no significant updates on the latter three entities in WHO-HAEM5. In contrast, the entity of **follicular lymphoma** has undergone significant revision. The vast majority of FL (85%) have at least in part a follicular growth pattern, are composed of centrocytes and centroblasts and harbour the t(14;18)(q32;q21) translocation associated with *IGH*::*BCL2* fusion; these are now termed **classic FL (cFL)** and set apart from two related subtypes/groups, **follicular large B-cell lymphoma (FLBL)** and **FL with uncommon features (uFL)**.

Leukemia (2022) 36:1720–1748; https://doi.org/10.1038/s41375-022-01620-2

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Linfoma follicolare

- WHO-5:
  - **non necessario grading** (non riproducibile e di scarso significato clinico)
  - Linfoma follicolare **a grandi cellule** (FL 3B)
  - FL 3A diffuso **non è più considerato DLBCL**
  - Linfoma follicolare „**classico**"
  - Linfoma follicolare „**non convenzionale**"
- ICC:
  - Grading mantenuto
  - miglioramento dei criteri per FL 3B (CD10-negativo, t(14;18)-negativo)

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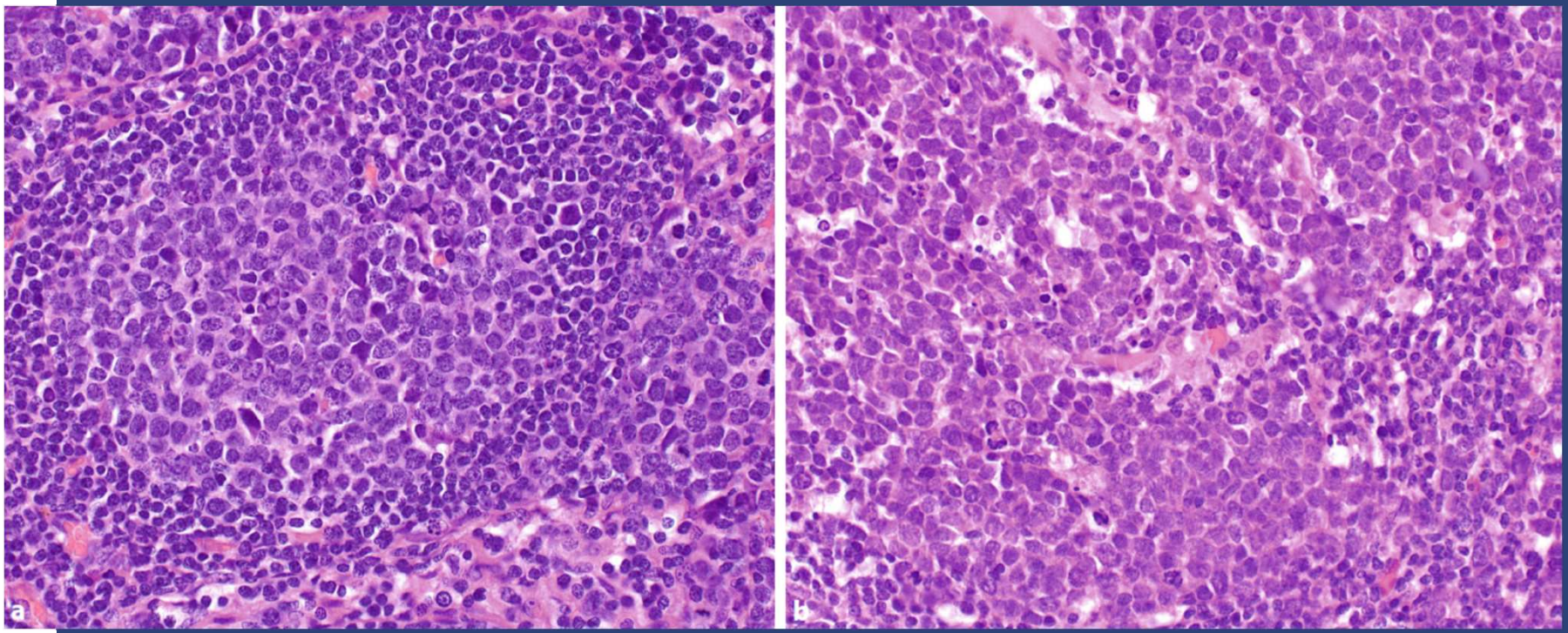
Linfoma follicolare a grandi cellule (solo WHO - ex 3B)



Leukemia (2023) 37:18–34; https://doi.org/10.1038/s41375-022-01764-1

Linfoma follicolare non convenzionale (WHO-5)

- Variante „blastoide“ o con „grossi centrociti“
- Variante a crescita prevalentemente diffusa

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Linfoma follicolare non convenzionale (WHO-5)

The newly introduced subtype of uFL includes two subsets that significantly diverge from cFL: one with "blastoid" or "large centrocyte" variant cytological features, and the other with a predominantly diffuse growth pattern [104, 105]. FL with "blastoid" or "large centrocyte" cytological features more frequently display variant immunophenotypic and genotypic characteristics and may show inferior survival [106]. They need to be

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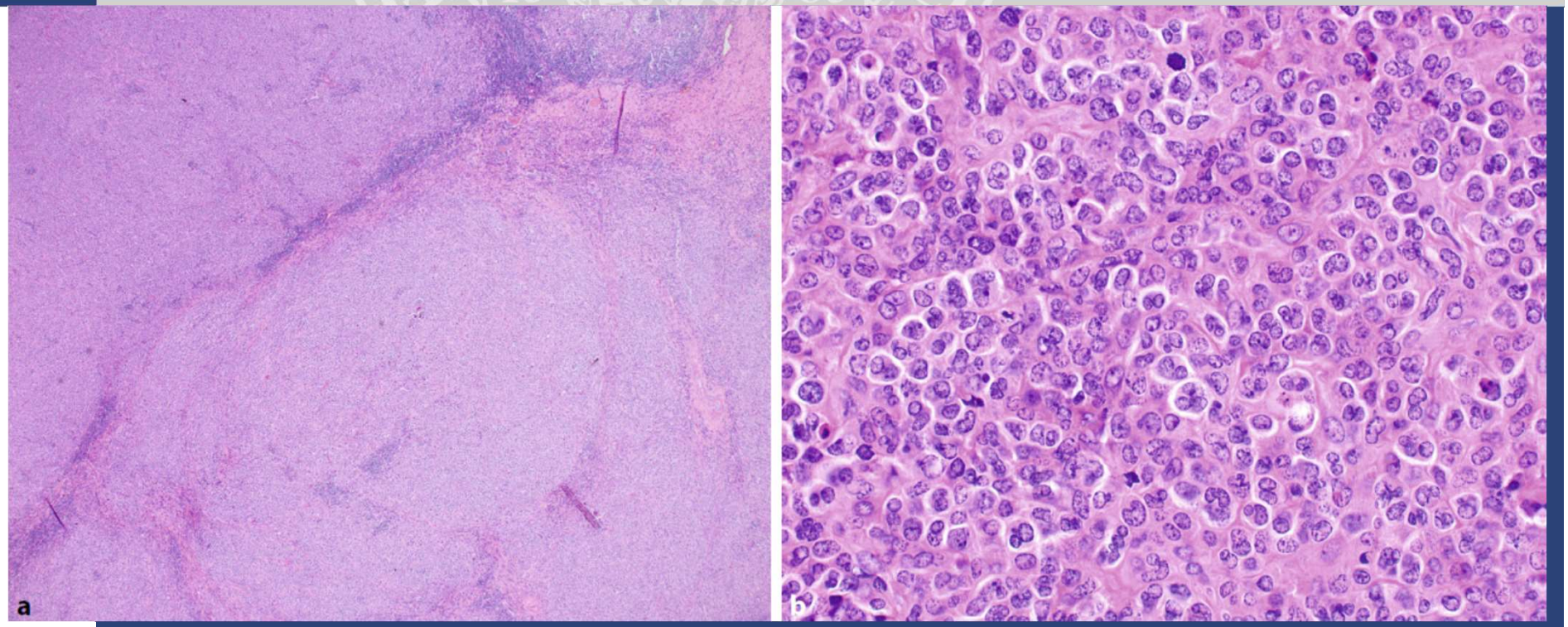
Linfoma follicolare non convenzionale (WHO-5)



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FL non convenzionale (WHO-5)
Linfoma del centro germinativo BCL2-R-negativo, CD23-positivo (ICC – entità provvisoria)

ment [107]. FL with a predominantly diffuse growth pattern frequently occurs as a large tumour in the inguinal region and is associated with CD23 expression, an absence of *IGH::BCL2* fusion [108], and frequent *STAT6* mutations along with 1p36 deletion or *TNFRSF14* mutation [104, 109]. Separating such cases from cFL will support research to clarify disease biology, allowing a better definition in future classifications.

A distinctive subtype of t(14;18)-negative nodal follicular non-Hodgkin lymphoma characterized by a predominantly diffuse growth pattern and deletions in the chromosomal region 1p36

Tiemo Katzenberger,[1] Jörg Kalla,[1] Ellen Leich,[1] Heike Stöcklein,[1,2] Elena Hartmann,[1] Sandra Barnickel,[1] Swen Wessendorf,[3] M. Michaela Ott,[4] Hans Konrad Müller-Hermelink,[1] *Andreas Rosenwald,[1] and *German Ott[1,2]

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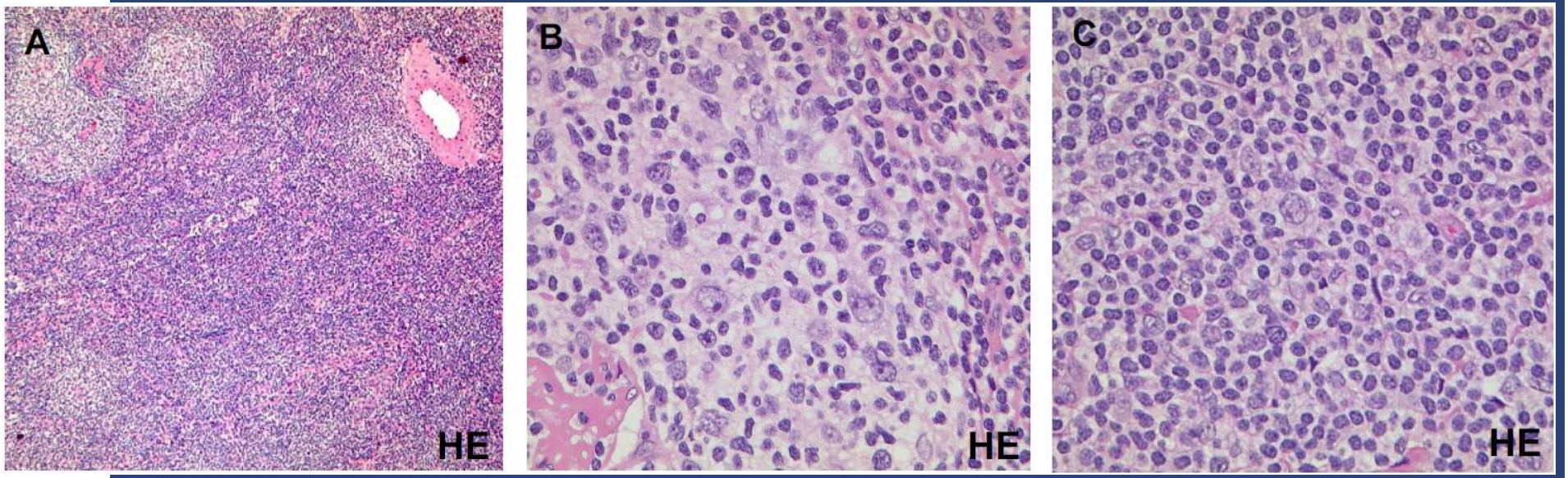

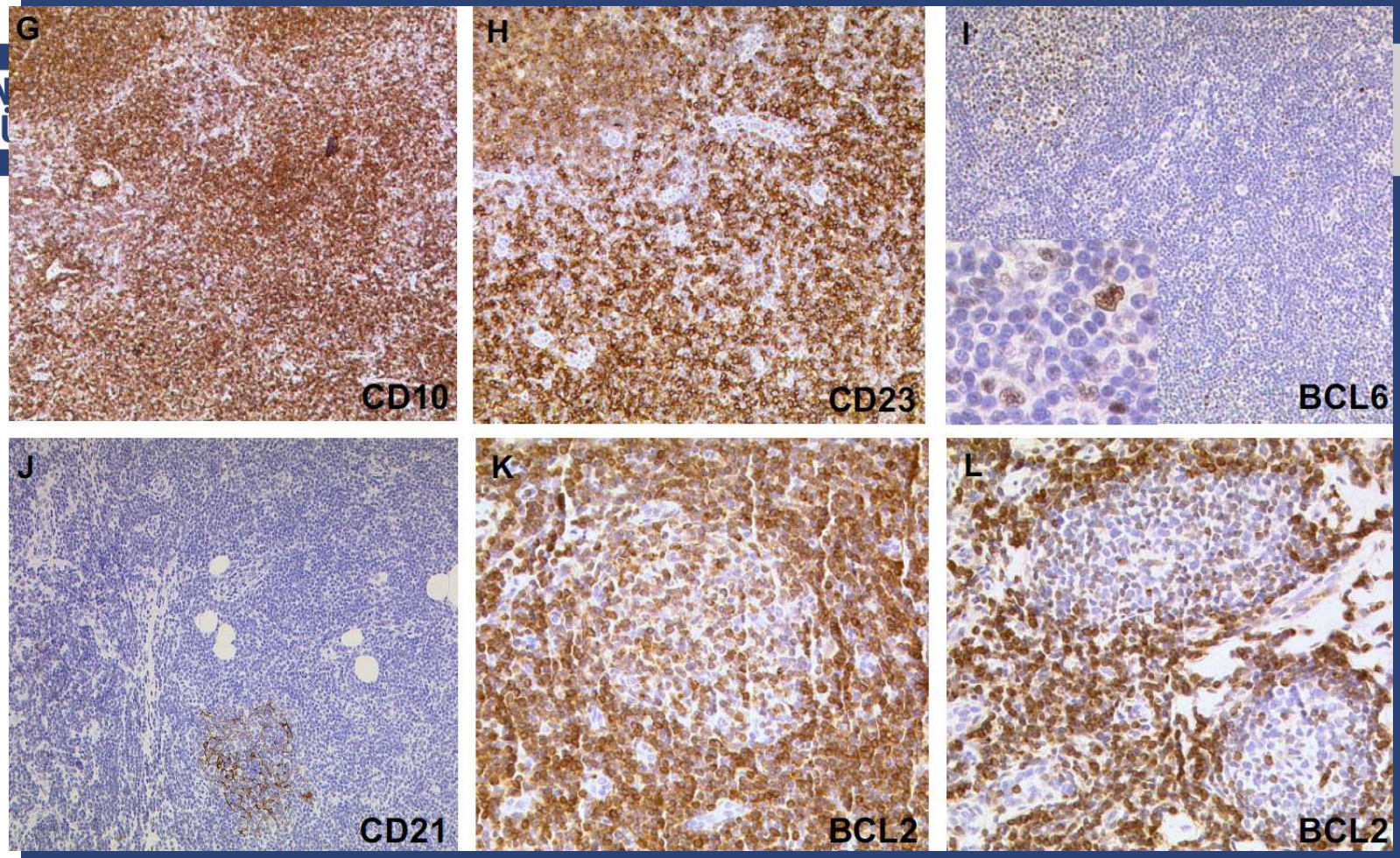

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Linfoma del CG diffuso BCL2-R-negativo CD23-positivo (linfoma di Katzenberger/Ott)

- Frequentemente inguinale, stadio I-II
- Morfologia ed immunofenotipo caratteristici
- Frequenti (>80%) mutazioni di STAT6 e CREBBP*

*Siddiqui et al. Mod Pathol. 2016 Jun;29(6):570-81
*Zamò et al. Br J Haematol. 2018 Feb;180(3):391-394

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WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Diffuse follicular lymphoma variant (not considered an entity)	FL with predominantly diffuse pattern (not considered an entity)	BCL2-R-negative, CD23-positive follicle center lymphoma (provisional entity)
Primary cutaneous follicle center lymphoma	Primary cutaneous follicle center lymphoma	Primary cutaneous follicle center lymphoma
Pediatric-type follicular lymphoma	Pediatric-type follicular lymphoma	Pediatric-type follicular lymphoma
Testicular follicular lymphoma	Not considered an entity →	Testicular follicular lymphoma (distinct entity)
Large B-cell lymphoma with IRF4 rearrangement (provisional entity)	Large B-cell lymphoma with *IRF4* rearrangement (upgraded to distinct entity) →	Large B-cell lymphoma with *IRF4* rearrangement (upgraded to a distinct entity)

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J Pediatr Hematol Oncol • Volume 26, Number 2, February 2004

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Primary Follicular Lymphoma of the Testis

Excellent Outcome Following Surgical Resection Without Adjuvant Chemotherapy

Kevin N. Heller, MD, Julie Teruya-Feldstein, MD,† Michael P. La Quaglia, MD,*‡ and Leonard H. Wexler, MD**

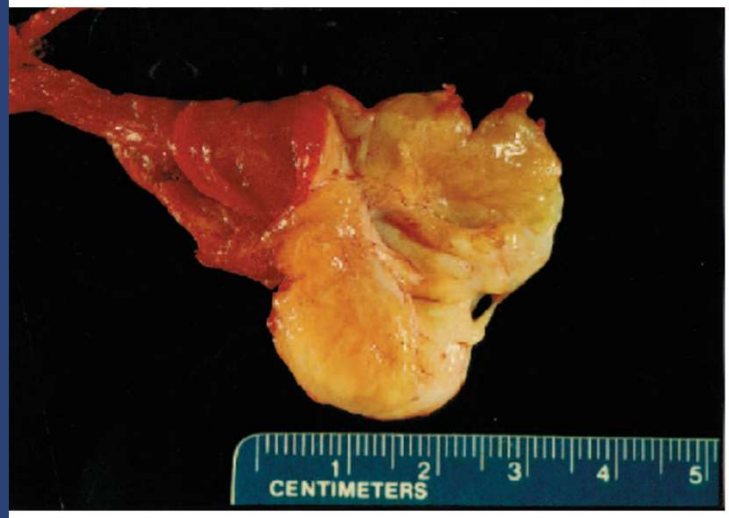

FIGURE 1. Gross photograph of the left testicle removed by left radical orchiectomy. Cut surface shows a homogeneous tan surface without necrosis and hemorrhage.

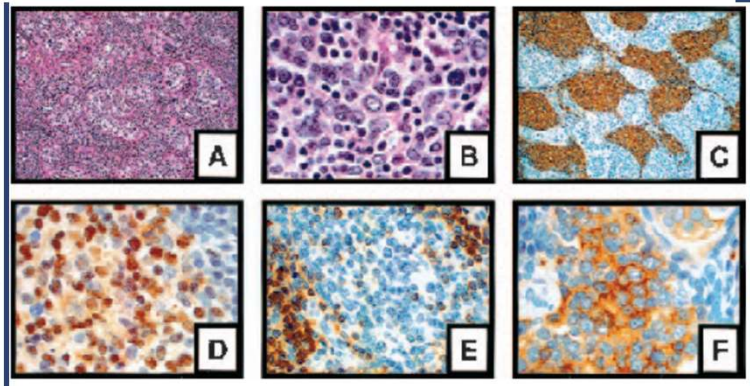

FIGURE 2. Microscopic sections showed a dense lymphoid infiltrate with a vague nodular growth pattern infiltrating seminiferous tubules (**A**, 10× magnification), with large lymphoid cells having open chromatin and distinct nucleoli (**B**, 40×). Tumor cells were positive for CD20 (**C**), BCL6 (**D**), and CD10 (**F**) but negative for BCL2 (**E**), diagnostic of follicular lymphoma, grade 3 of 3.

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Linfoma follicolare primitivo del testicolo (solo ICC)

- Pazienti prevalentemente in età pediatrica
- Stadio IE, LDH normale o lievemente aumentato
- Curabile con orchiectomia +/- RT +/- CT
- Grado 3A, possibili aree diffuse, fenotipo GCB
- t(14;18)-negativo
- Frequenti mutationi di TNFRSF14 e MAP2K1
- DD: DLBCL del testicolo (ABC, MYD88/CD79a-M, BCL2++)

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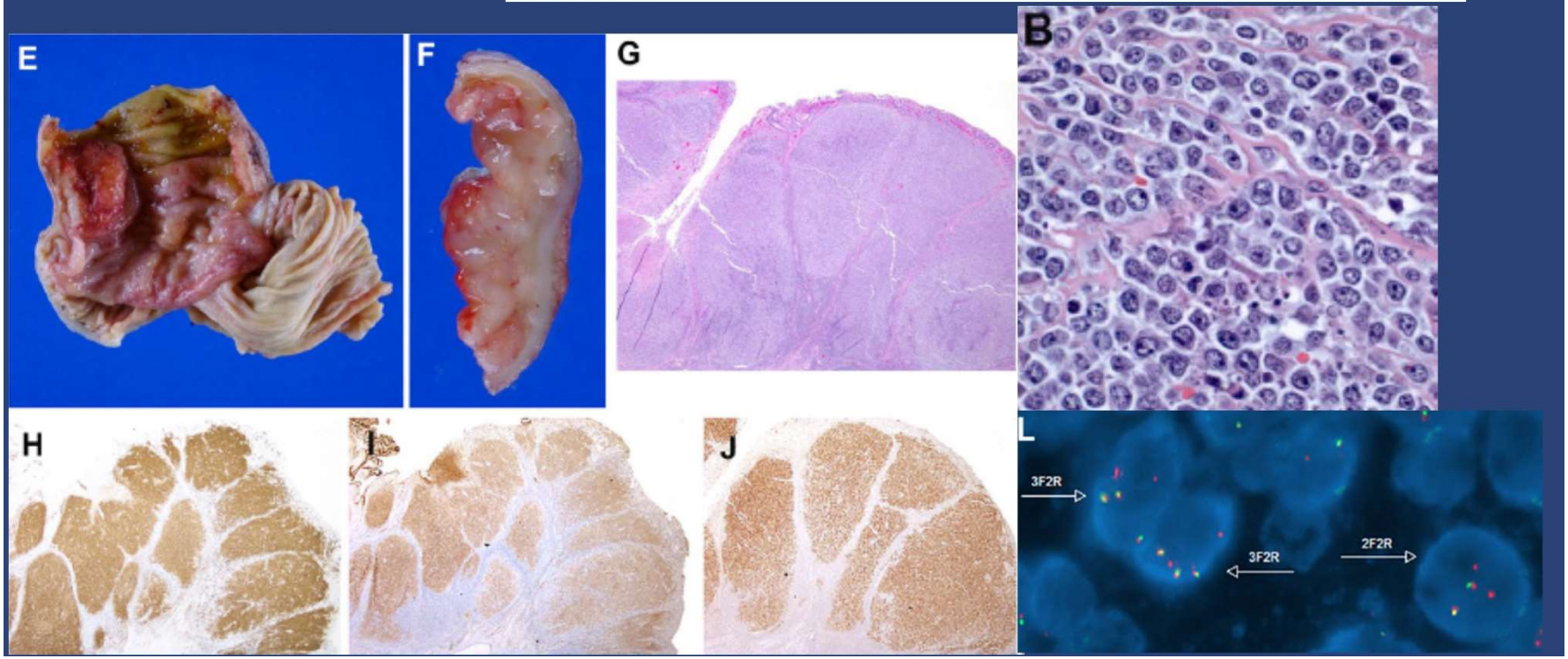
https://doi.org/10.1007/s00428-023-03590-x

Emerging entities: high-grade/large B-cell lymphoma with 11q aberration, large B-cell lymphoma with *IRF4* rearrangement, and new molecular subgroups in large B-cell lymphomas. A report of the 2022 EA4HP/SH lymphoma workshop

Leticia Quintanilla-Martinez[1,2] · Camille Laurent[3] · Lorinda Soma[4] · Siok-Bian Ng[5,6] · Fina Climent[7] · Sarah L. Ondrejka[8] · Alberto Zamo[9] · Andrew Wotherspoon[10] · Laurence de Leval[11] · Stefan Dirnhofer[12] · Lorenzo Leoncini[13]



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Linfoma B a grandi cellule con riarrangiamento di IRF4

- Giovani adulti
- Prevalentemente cervicale e anello del Waldeyer, stadio I-II
- Morfologia: FL 3A/B +/- DLBCL
- IHC: 80% triplo positivo (CD10+, BCL6+, MUM1/IRF4+), freq. CD5+
- Genetica: MYC-R-negativo, IRF4-R-positivo, freq. BCL6-R-positivo, mutazioni in IRF4

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Linfomi della zona marginale

WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Not considered as an entity	Primary cutaneous marginal zone lymphoma (new entity)	Primary cutaneous marginal zone lymphoproliferative disorder (distinct entity)
Nodal marginal zone lymphoma	Nodal marginal zone lymphoma	Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma (provisional)	Pediatric marginal zone lymphoma (distinct entity)	Pediatric nodal marginal zone lymphoma (provisional)

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Linfoma della zone marginale primitivo cutaneo (WHO)
Disordine linfoproliferativo della zona marginale primitivo cutaneo (ICC)

- Viene riconosciuto il comportamento clinico indolente con recidive locali ma quasi mai disseminazione sistemica

(in analogia al disordine proliferativo T CD4-positivo a piccole e medie cellule)

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Linfoma marginale (nodale) di tipo pediatrico

- WHO-5: entità distinta
- ICC: entità provvisoria (sottolineata la convergenza con il linfoma follicolare di tipo pediatrico – mutazioni simili es. TNFRSF14, IRF8, MAP2K1)

- DD: iperplasia follicolare atipica da H. influenzae

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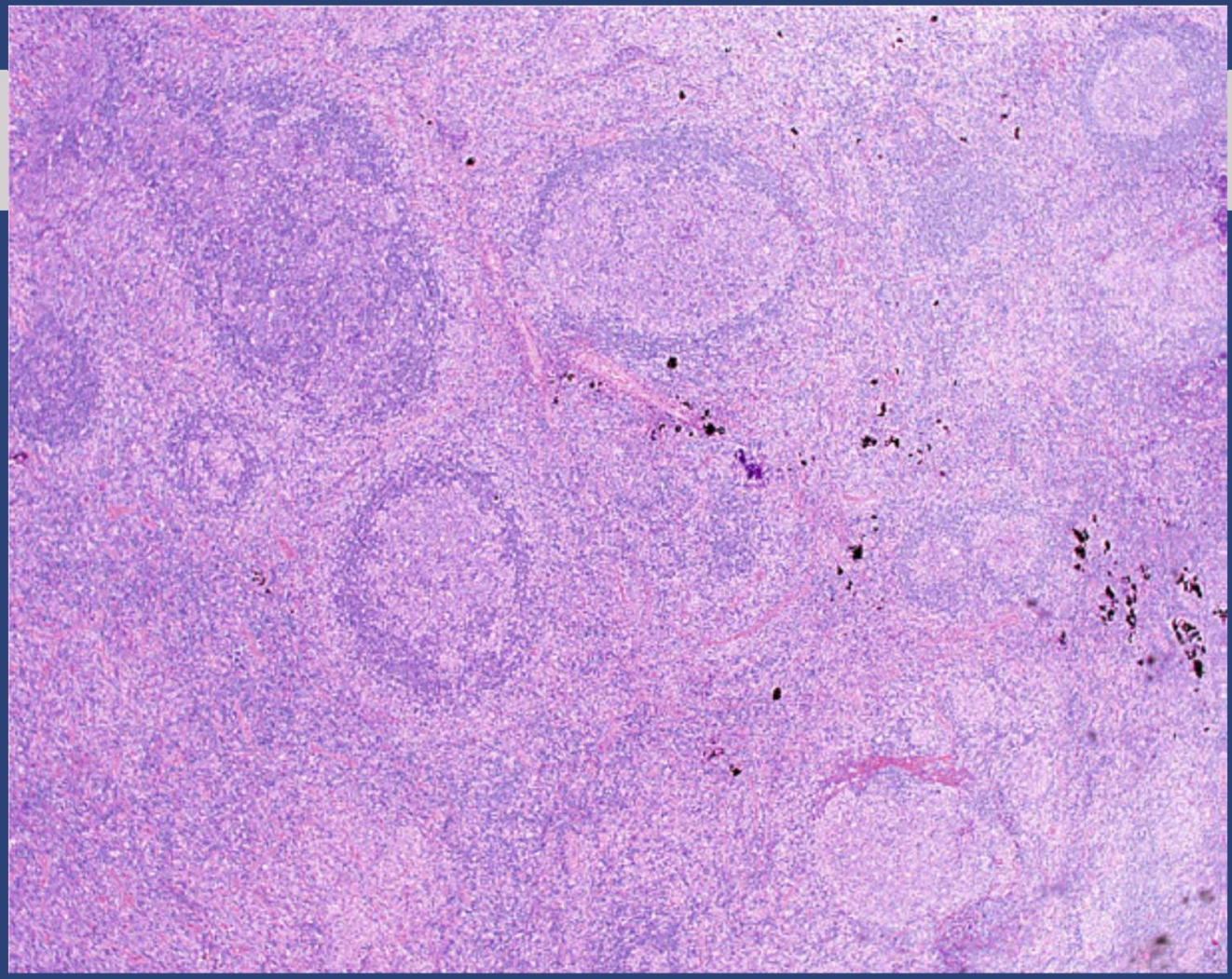

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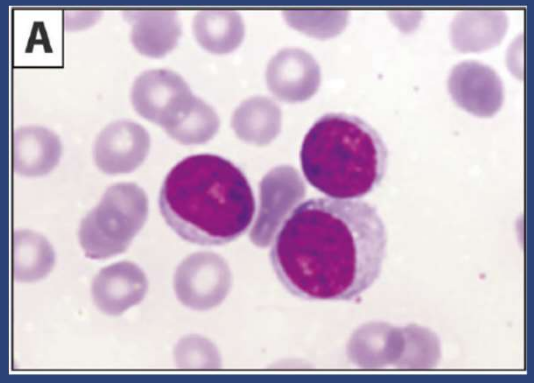
Linfomi splenici/midollari

WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Splenic marginal zone lymphoma	Splenic marginal zone lymphoma	Splenic marginal zone lymphoma
Hairy cell leukemia	Hairy cell leukemia	Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable	Splenic diffuse red pulp small B-cell lymphoma	Splenic B-cell lymphoma/leukemia, unclassifiable
- Splenic diffuse red pulp small B-cell lymphoma (provisional)	Splenic B-cell lymphoma/leukemia with prominent nucleoli (also includes hairy cell leukemia-variant and cases of B-cell prolymphocytic leukemia)	- Splenic diffuse red pulp small B-cell lymphoma (provisional)
- Hairy cell leukemia-variant (provisional)		- Hairy cell leukemia-variant (provisional)

Leukemia (2023) 37:18–34; https://doi.org/10.1038/s41375-022-01764-1

WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Monoclonal B-cell lymphocytosis	Monoclonal B-cell lymphocytosis	Monoclonal B-cell lymphocytosis
CLL-type (low and high count)	Low-count or clonal B-cell expansion	CLL-type (low and high count)
	CLL/SLL-type	
- Non-CLL-type	Non-CLL/SLL-type	- Non-CLL-type
- Atypical CLL-type		- Atypical CLL-type
Chronic lymphocytic leukemia /small lymphocytic lymphoma	Chronic lymphocytic leukemia/small lymphocytic lymphoma	Chronic lymphocytic leukemia /small lymphocytic lymphoma
B-cell prolymphocytic leukemia	Entity deleted (renamed Splenic B-cell lymphoma/ leukemia with prominent nucleoli)	B-cell prolymphocytic leukemia



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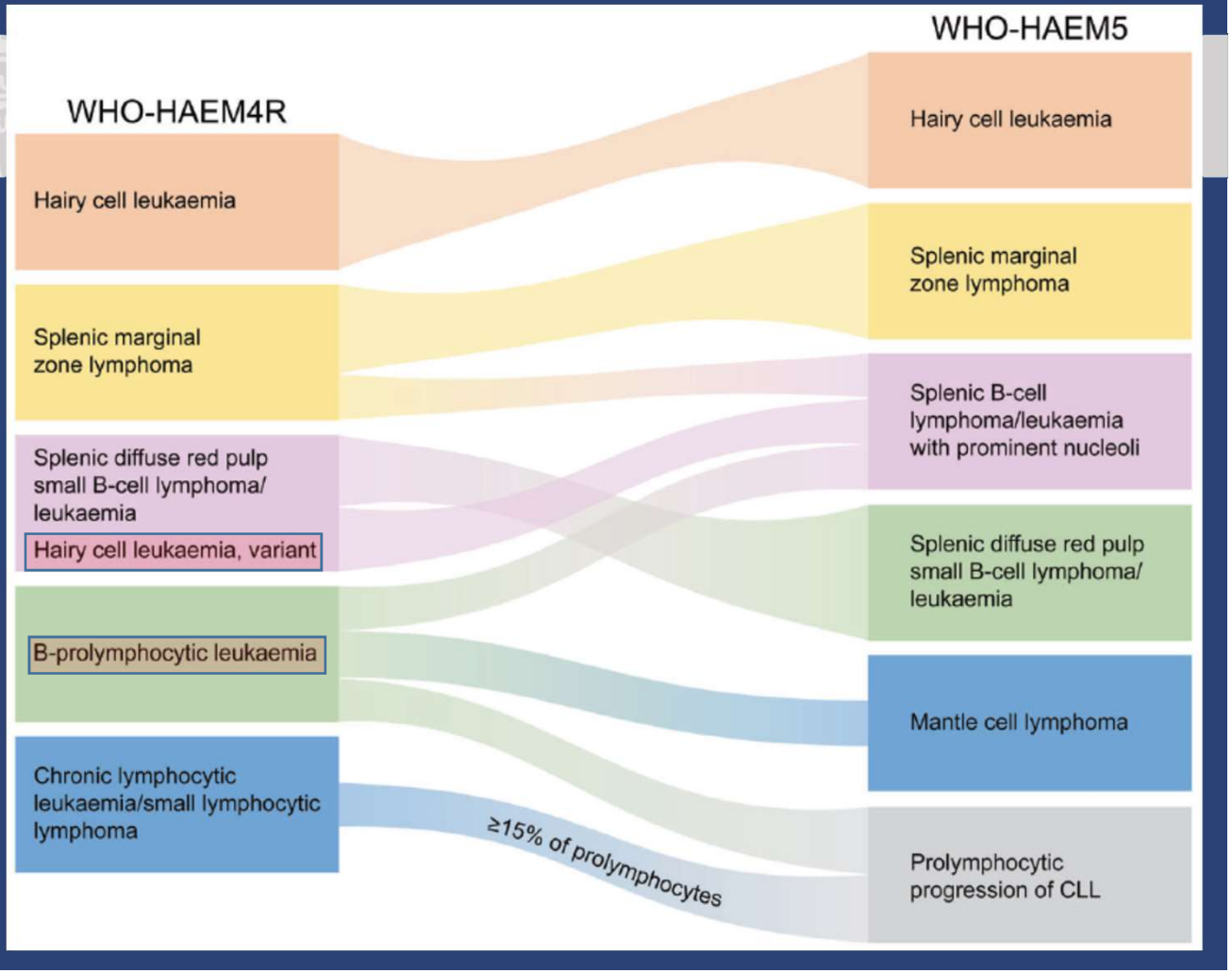

Leukemia (2022) 36:1720 – 1748

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Take-home message 1 – linfomi B „indolenti“

- Migliorati i criteri diagnostici
- Grading nel FL perde di importanza
- Definizione di entità pediatriche/giovanili rare, con buona prognosi, tuttavia confondibili con DLBCL (FISH e genetica di fondamentale importanza)
- Nella WHO scompare la B-PLL

Linfomi B „aggressivi“

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WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Transformations of indolent B-cell lymphomas		
Not included as an entity	Transformations of indolent B-cell lymphomas	Not included as an entity
Large B-cell lymphomas		
Diffuse large B-cell lymphoma, NOS	Diffuse large B-cell lymphoma, NOS	Diffuse Large B-cell lymphoma, NOS
- Germinal Center B-cell subtype	- Recommended	- Germinal Center B-cell subtype
- Activated B-cell subtype	- Recommended	- Activated B-cell subtype
Burkitt-like lymphoma with 11q aberration (provisional entity)	High grade B-cell lymphoma with 11q aberrations	Large B-cell lymphoma with 11q aberration (provisional entity)
Large B-cell lymphoma with IRF4 rearrangement (provisional entity)	Large B-cell lymphoma with *IRF4* rearrangement (upgraded to distinct entity)	Large B-cell lymphoma with *IRF4* rearrangement (upgraded to a distinct entity)

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Virchows Archiv (2023) 483:281–298

High grade (WHO) / large cell (ICC) lymphoma with 11q aberrations

- Prevalentemente giovani, possibile anche in anziani
- Morfologia variabile (spesso Burkitt-simile)
- Immunofenotipo Burkitt-simile
- MYC-R-negativo
- 11q23 gain + 11q24 loss
- Mutazioni più simili a DLBCL (50% GNA13)

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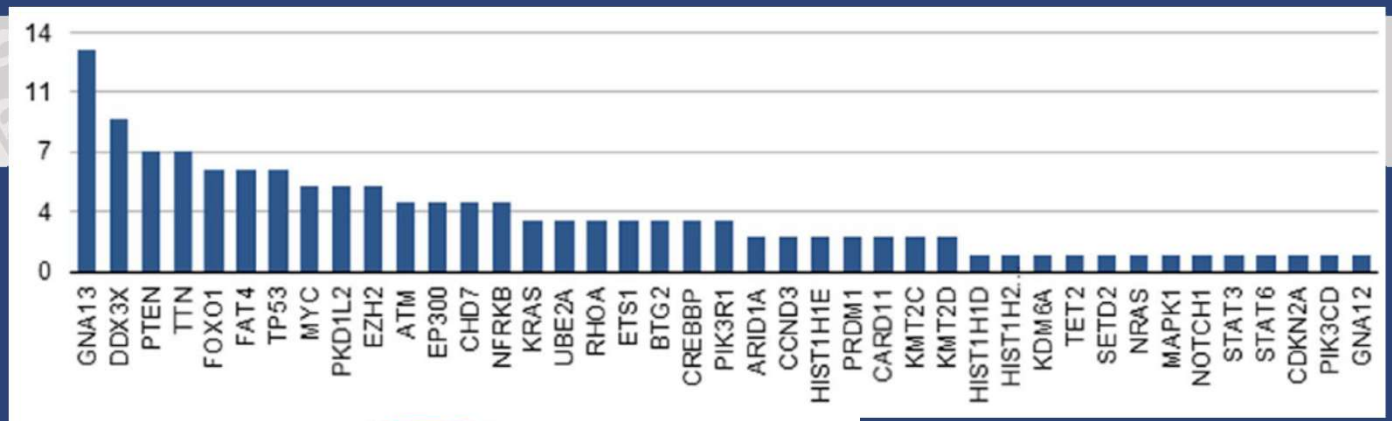
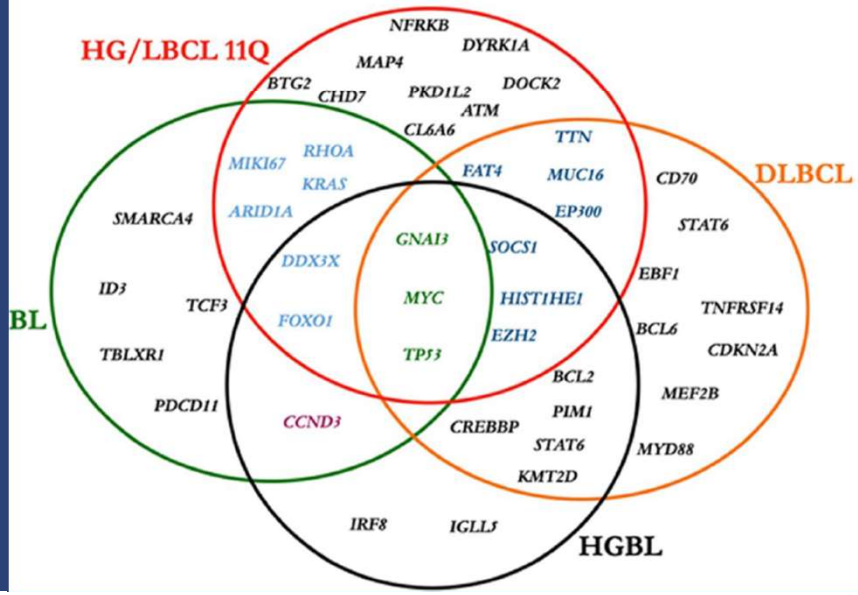
Virchows Archiv (2023) 483:281–298





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WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
	Primary large B-cell lymphoma of immune-privileged sites	
- Primary diffuse large B-cell lymphoma of CNS	- Primary large B-cell lymphoma of CNS	- Primary diffuse large B-cell lymphoma of CNS
- Not considered as an entity	- Primary large B-cell lymphoma of testis (new entity)	- Primary diffuse large B-cell lymphoma of testis (new entity)
- Reported in primary diffuse large B-cell lymphoma of CNS	- Primary large B-cell lymphoma of vitreoretina	- Included in primary diffuse large B-cell lymphoma of CNS
Primary cutaneous diffuse large B-cell lymphoma, leg type	Primary cutaneous diffuse large B-cell lymphoma, leg type	Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma

Leukemia (2023) 37:18–34; https://doi.org/10.1038/s41375-022-01764-1

Leukemia (2022) 36:1720 – 1748

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Table 4. Distinctive features of primary large B-cell lymphomas of immune privileged sites.

Subtypes	Primary large B-cell lymphoma → CNS
	Primary large B-cell lymphoma → vitreoretina
	Primary large B-cell lymphoma → testis
Clinical	Usually in adults over age of 60 years
	Lymphoma tends to "home" to other immune privileged sites: vitreoretina tumour may occur concurrently with or follow CNS tumour; testicular tumour tends to relapse in CNS or contralateral testis
	Aggressive tumours with generally poor prognosis
Morphology	Large B-cell lymphoma
Immunophenotype	Activated B-cell immunophenotype: Usually CD10-, MUM1+, BCL6+
	EBV negative
Mutational profile	Concomitant *MYD88* and *CD79B* mutations
	Immune evasion: genetic inactivation of MHC class I and II and *B2M* (β_2-microglobulin) with subsequent loss of protein expression
	Showing DLBCL genomic signature C5/MCD/MYD88

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WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Not included as an entity	Fluid overload-associated large B-cell lymphoma (ne entity)	HHV8 and EBV-negative primary effusion-based lymphoma (provisional entity)
Epstein-Barr virus-positive mucocutaneous ulcer (provisional entity)	Epstein-Barr virus-positive mucocutaneous ulcer (not included in this category; see lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation)	Epstein-Barr virus-positive mucocutaneous ulcer (upgraded to distinct entity)
EBV-positive diffuse large B-cell lymphoma, NOS	EBV-positive diffuse large B-cell lymphoma	EBV-positive diffuse large B-cell lymphoma, NOS

Leukemia (2023) 37:18–34; https://doi.org/10.1038/s41375-022-01764-1

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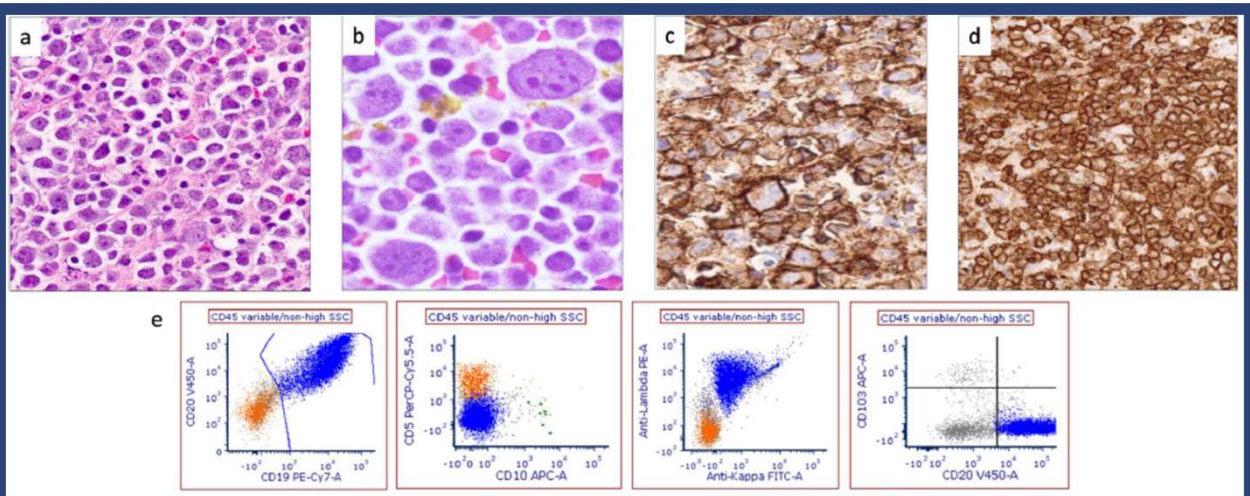
Virchows Archiv (2023) 483:299–316

Cavity-based lymphomas: challenges and novel concepts. A report of the 2022 EA4HP/SH lymphoma workshop

Arianna Di Napoli[1] · Lori Soma[2] · Leticia Quintanilla-Martinez[3] · Laurence de Leval[4] · Lorenzo Leoncini[5] · Alberto Zamò[6] · Siok-Bian Ng[7] · Sarah L. Ondrejka[8] · Fina Climent[9] · Andrew Wotherspoon[10] · Stefan Dirnhofer[11]

	EAHP-SH WS 2022 EBV-negative B-cell phenotype, effusion only ($n = 7$)
M:F	2:5
Median age	80
HIV	0/3 (0%)
HCV	NR
Pleural effusion	6/7 (86%)
Pericardial effusion	4/7 (57%)
Peritoneal effusion	0/7 (0%)
Clinical setting of fluid overload	7/7 (100%)
EBV+	0/7 (0%)
Immune def/supp	
CD20+	7/7 (100%)
CD10+	1/7 (14%)
MUM1+	6/6 (100%)
CD138+	2/5 (40%)
MYC rea	0/5 (0%)
BCL2 rea	0/4 (0%)
BCL6 rea	3/4 (75%)
Double or triple hit	0/4 (0%)
Mutations	CCND3, CD58, CREBBP, IGLL5, KLHL6, MAP2K1, MYD88, NFKBIA, NOTCH2, PIK3CA, PIM1, PRDM1, RB1, TNFAIP3, ZNF292 (n=2)



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Gene	Alteration	Classification	VAF
MYD88	p.L265P	Tier I	51%
PRDM1	p.L377fs*1	Tier II	41%
KLHL6	p.D73H	Tier II	40%
CREBBP	p.I612V	Tier II	37%
PIM1	p.L182F	Tier II	9%
PIM1	p.E135K	Tier II	3%

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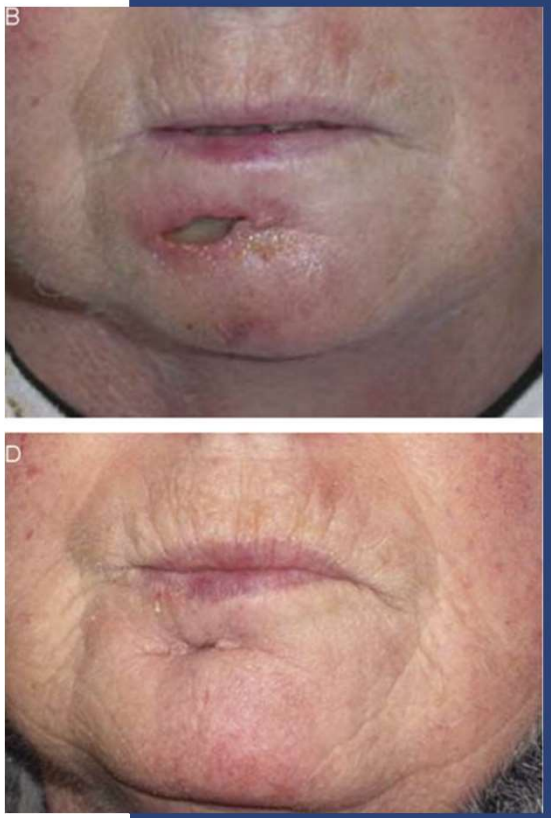
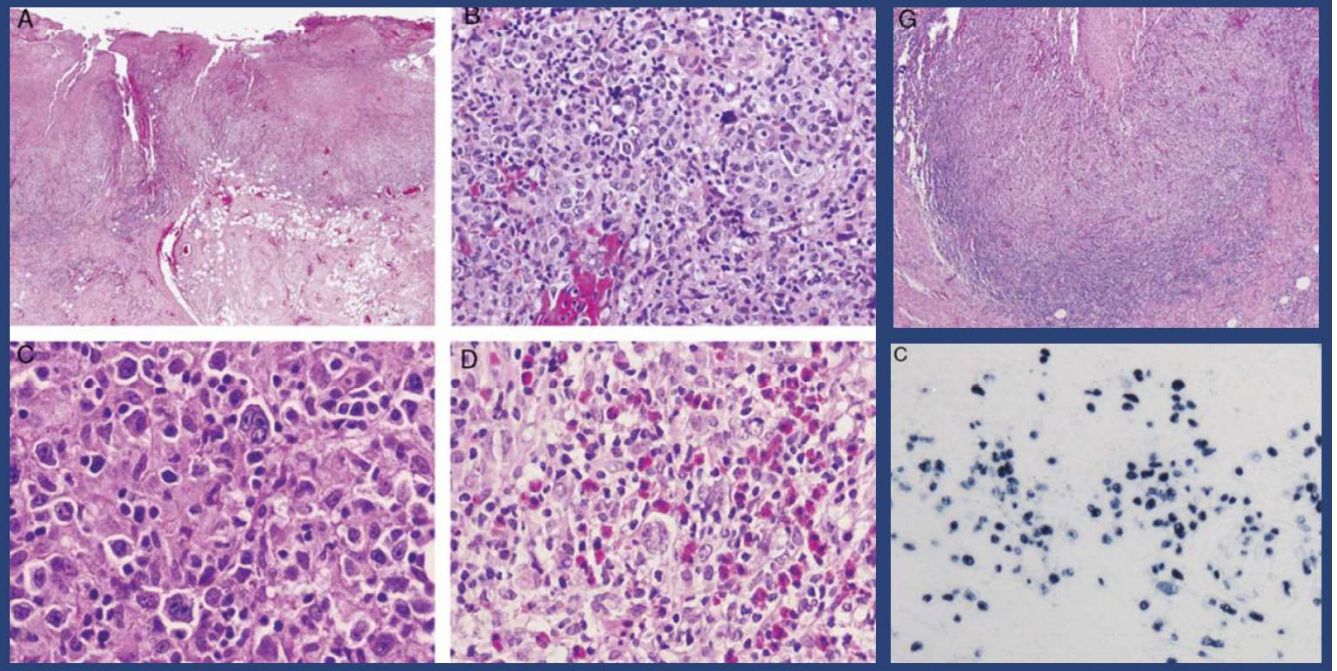
EBV Positive Mucocutaneous Ulcer—A Study of 26 Cases Associated With Various Sources of Immunosuppression

Stefan D. Dojcinov, MD, FRCPath, Girish Venkataraman, MD,†*
Mark Raffeld, MD,† Stefania Pittaluga, MD, PhD,† and Elaine S. Jaffe, MD†

Am J Surg Pathol 2010;34:405–417





WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Diffuse large B-cell lymphoma associated with chronic inflammation	Diffuse large B-cell lymphoma associated with chronic inflammation	Diffuse large B-cell lymphoma associated with chronic inflammation
Fibrin-associated large B-cell lymphoma (subtype of DLBCL associated with chronic inflammation)	Fibrin-associated large B-cell lymphoma (new entity)	Fibrin-associated large B-cell lymphoma (subtype of DLBCL associated with chronic inflammation)
Lymphomatoid granulomatosis	Lymphomatoid granulomatosis	Lymphomatoid granulomatosis
Not included as an entity	Described in Lymphoid proliferations/lymphomas associated with immune deficiency and dysregulation (not considered as an entity)	EBV positive polymohrphic B cell lymphoproliferative disorder, NOS (provisional entity)
ALK-positive large B-cell lymphoma	ALK-positive large B-cell lymphoma	ALK-positive large B-cell lymphoma
Plasmablastic lymphoma	Plasmablastic lymphoma	Plasmablastic lymphoma
High grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements	Diffuse large B-cell lymphoma/High grade B-cell lymphoma with *MYC* and *BCL2* rearrangements	High grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
Not included as an entity	Not included as an entity	High grade B-cell lymphoma with MYC and BCL6 rearrangements (provisional entity)
High-grade B-cell lymphoma, NOS	High-grade B-cell lymphoma, NOS	High-grade B-cell lymphoma, NOS
Primary mediastinal B-cell lymphoma	Primary mediastinal B-cell lymphoma	Primary mediastinal B-cell lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Classic Hodgkin lymphoma	Mediastinal gray zone lymphoma	Mediastinal gray zone lymphoma

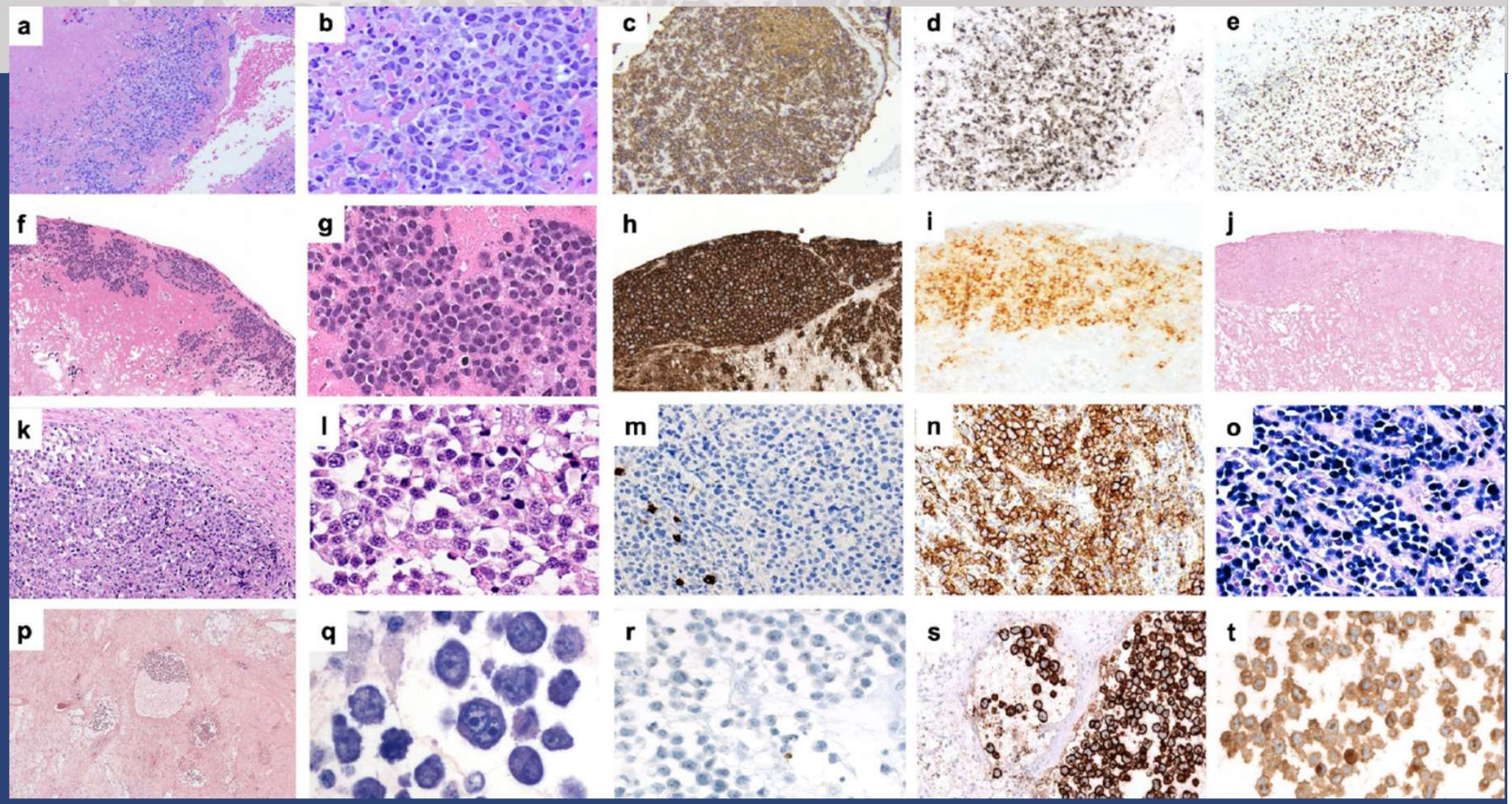
Leukemia (2023) 37:18–34; https://doi.org/10.1038/s41375-022-01764-1

Virchows Archiv (2023) 483:299–316

Table 4 Characteristics of the EAHP-SH workshop fibrin-associated diffuse large B-cell lymphoma cases

Site	Cardiac myxoma ($n = 3$)	Thrombus ($n = 7$) - valves ($n = 2$) - vascular ($n = 5$)	Cyst/pseudocyst ($n = 10$) - Adrenal ($n = 2$) - Hepatic ($n = 1$) - GIST ($n = 1$) - Pacemaker pocket ($n = 1$) - Breast implant ($n = 5$)
M:F	1:2	6:1	3:5 (2 NR)
Median age (range)	60 (50–76)	72 (23–76)	61 (45–72)
Graft/foreign body	-	4/7 (57%)	6/9 (67%)
Median time from implantation (years) (range)	-	14.5 (0.6-23)	12.5 (1.6-26)
HIV	NR	NR	1 (HIV+) 9 (NR)
EBV+	0/3 (0%)	7/7 (100%)	9/10 (90%)
CD20 +	3/3 (100%)	6/7 (1 partial) (86%)	8/10 (1 partial) (80%)
CD10+	2/3 (67%)	0/7 (0%)	0/5 (0%)
MUM1+	1/3 (33%)	7/7 (100%)	8/8 (100%)
CD138+	NR	0/2 (0%)	4/4 (1 partial) (100%)
CD30+	0/2 (0%)	4 (3 partial)/6 (67%)	7/10 (1 partial) (70%)
PD-L1+	0/1 (0%)	1/1 (100%)	2/2 (100%)
MYC rea	0/3 (0%)	0/3 (0%)	1/3 (33%)
BCL2 rea	0/3 (0%)	0/3 (0%)	0/3 (0%)
BCL6 rea	1/3 (33%)	0/2 (0%)	0/3 (0%)
Mutations	BCL11A, CARD11, CD58, CD79B, CREBBP, ETV6, HIST1H1E, HIST1H2BD, HIST1H1D; HLA-B, IKZF3, NOTCH1, PAX5, PIM1 (n=2)		BTG1, CXCR4, KMT2D, MEF2B (n=1)

Virchows Archiv (2023) 483:299–316



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WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
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Fibrin-associated large B-cell lymphoma (subtype of DLBCL associated with chronic inflammation)	Fibrin-associated large B-cell lymphoma (new entity)	Fibrin-associated large B-cell lymphoma (subtype of DLBCL associated with chronic inflammation)
Lymphomatoid granulomatosis	Lymphomatoid granulomatosis	Lymphomatoid granulomatosis
Not included as an entity	Described in Lymphoid proliferations/lymphomas associated with immune deficiency and dysregulation (not considered as an entity)	EBV positive polymohrphic B cell lymphoproliferative disorder, NOS (provisional entity)
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Plasmablastic lymphoma	Plasmablastic lymphoma	Plasmablastic lymphoma
High grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements →	Diffuse large B-cell lymphoma/High grade B-cell lymphoma with *MYC* and *BCL2* rearrangements →	High grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
Not included as an entity →	Not included as an entity →	High grade B-cell lymphoma with MYC and BCL6 rearrangements (provisional entity)
High-grade B-cell lymphoma, NOS	High-grade B-cell lymphoma, NOS	High-grade B-cell lymphoma, NOS
Primary mediastinal B-cell lymphoma	Primary mediastinal B-cell lymphoma	Primary mediastinal B-cell lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Classic Hodgkin lymphoma	Mediastinal gray zone lymphoma	Mediastinal gray zone lymphoma

Leukemia (2023) 37:18–34; https://doi.org/10.1038/s41375-022-01764-1

Linfomi "double-hit"

- WHO: solo MYC+BCL2-R
- ICC: mantenuto MYC+BCL6 come entità provvisoria (sottotipo molecolare BN2?)

WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Diffuse large B-cell lymphoma associated with chronic inflammation	Diffuse large B-cell lymphoma associated with chronic inflammation	Diffuse large B-cell lymphoma associated with chronic inflammation
Fibrin-associated large B-cell lymphoma (subtype of DLBCL associated with chronic inflammation)	Fibrin-associated large B-cell lymphoma (new entity)	Fibrin-associated large B-cell lymphoma (subtype of DLBCL associated with chronic inflammation)
Lymphomatoid granulomatosis	Lymphomatoid granulomatosis	Lymphomatoid granulomatosis
Not included as an entity	Described in Lymphoid proliferations/lymphomas associated with immune deficiency and dysregulation (not considered as an entity)	EBV positive polymohrphic B cell lymphoproliferative disorder, NOS (provisional entity)
ALK-positive large B-cell lymphoma	ALK-positive large B-cell lymphoma	ALK-positive large B-cell lymphoma
Plasmablastic lymphoma	Plasmablastic lymphoma	Plasmablastic lymphoma
High grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements	Diffuse large B-cell lymphoma/High grade B-cell lymphoma with *MYC* and *BCL2* rearrangements	High grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
Not included as an entity	Not included as an entity	High grade B-cell lymphoma with MYC and BCL6 rearrangements (provisional entity)
High-grade B-cell lymphoma, NOS	High-grade B-cell lymphoma, NOS	High-grade B-cell lymphoma, NOS
Primary mediastinal B-cell lymphoma	Primary mediastinal B-cell lymphoma	Primary mediastinal B-cell lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Classic Hodgkin lymphoma	Mediastinal gray zone lymphoma	Mediastinal gray zone lymphoma

Leukemia (2023) 37:18–34; https://doi.org/10.1038/s41375-022-01764-1

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Virchows Archiv (2023) 482:207–226

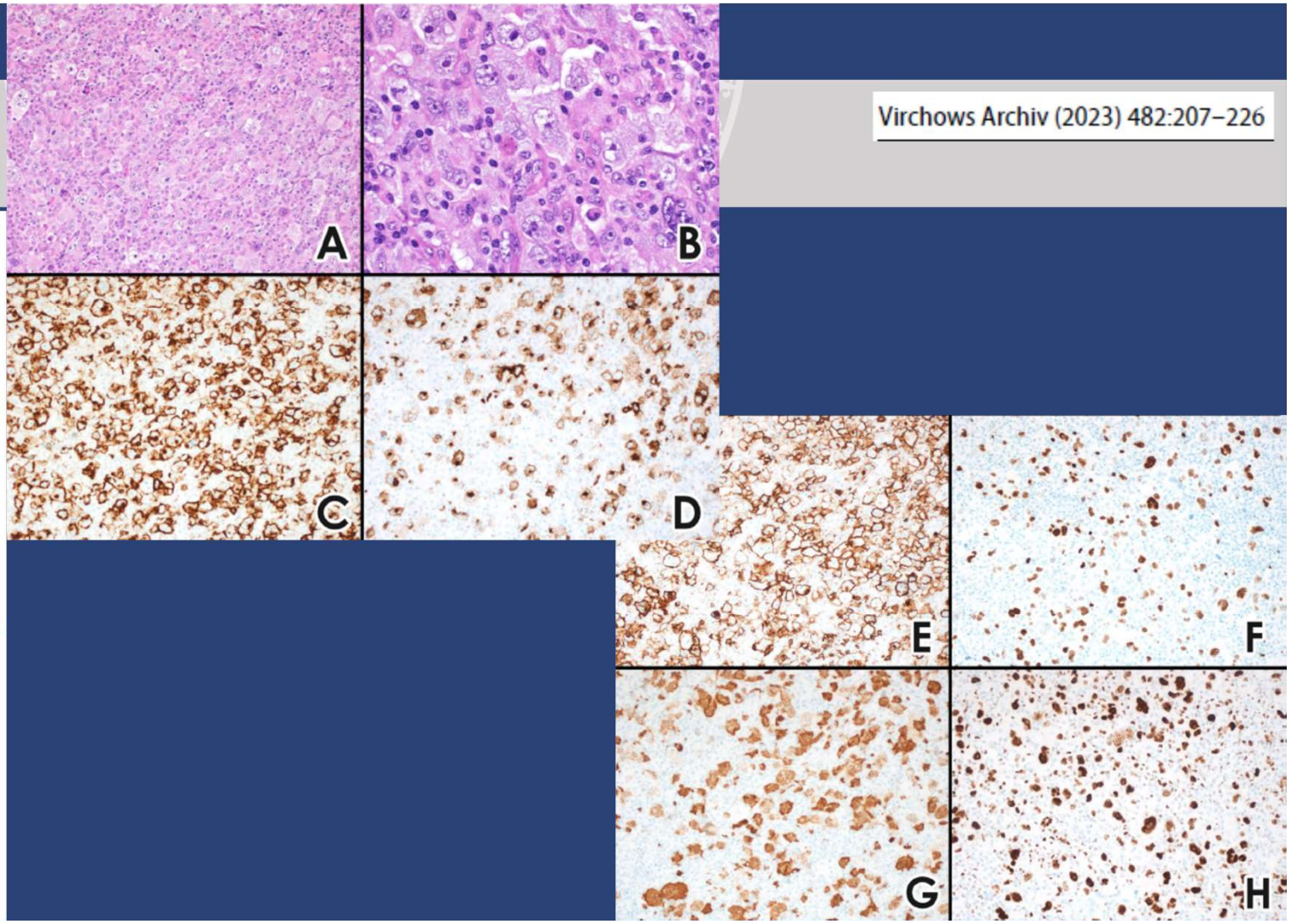

Fig. 3 Mediastinal gray zone lymphoma with a tumor cell-rich Hodgkin-like appearance. **A** Numerous tumor cells forming loose sheets within an inflammatory background. H&E, 200×. **B** Tumor cells are pleomorphic with lobulated nuclei and prominent nucleoli. Background cells are predominantly histiocytes and small lymphocytes. H&E, 600×oil. **C** CD30 shows strong diffuse staining, while CD15 (**D**) stains a subset of tumor cells. However, CD20 (**E**) is strongly and diffusely positive, which is atypical for classic Hodgkin lymphoma. Strong PAX5 (**F**), BOB1 (**G**), and OCT2 (**H**) emphasize a retained B cell transcriptional program. (All stains 200×)

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Take-home messages 2 – linfomi B aggressivi

- Definizione dei criteri per linfoma B con aberrazioni di 11q
- Definizione di DLBCL dei siti immunoprivilegiati
- Definizione del linfoma della zona grigia mediastinico
- Definizione di entità a **buona prognosi**: DLBCL fibrina-associato, DLBCL associato a sovraccarico di fluidi, ulcera muco-cutanea EBV-positiva

Linfomi T

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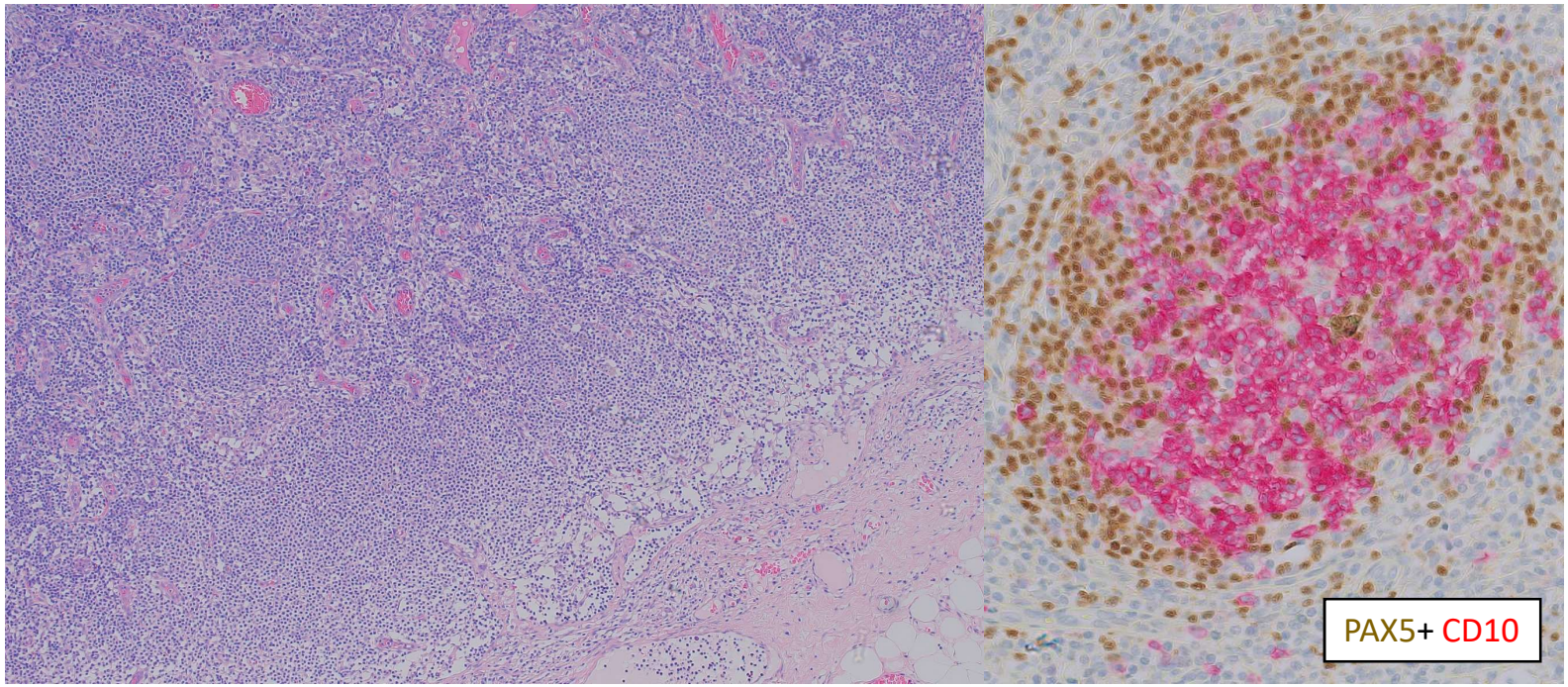
Linfomi anaplastici a grandi cellule

WHO-HAEM 4th revised edition	WHO-HAEM 5th edition 2022	ICC 2022
Anaplastic large cell lymphoma ALK positive	Anaplastic large cell lymphoma ALK positive	Anaplastic large cell lymphoma ALK positive
Anaplastic large cell lymphoma ALK negative	Anaplastic large cell lymphoma ALK negative	Anaplastic large cell lymphoma ALK negative **Molecular subtype**: *DUSP22*-R
Breast implant-associated anaplastic large cell lymphoma (provisional entity)	Breast implant-associated anaplastic large cell lymphoma	Breast implant-associated anaplastic large cell lymphoma

Gli ALCL **primitivi cutanei** sono raggruppati tra le proliferazioni linfoidi a cellule T **primitive cutaneee** , in considerazione della relazione clinico-patologica con questi disturbi e dell'esito altamente favorevole rispetto agli ALK- ALCL **sistemici**.

WHO-HAEM revised 4th edition	WHO-HAEM 5th edition 2022	ICC 2022
	Family of three nodal T-follicular helper cell lymphomas	Follicular helper T-cell lymphoma (**one entity**, three subtypes)
Angioimmunoblastic T-cell lymphoma	nTFHL-angioimmunoblastic type	TFH lymphoma, angioimmunoblastic type
Follicular T-cell lymphoma	nTFHL-follicular type	TFH lymphoma, follicular type
Nodal PTCL with TFH phenotype	nTFHL-not otherwise specified	TFH lymphoma, NOS

TFH lymphoma, follicular type



*Slide: courtesy of Prof. I. Anagnostopoulos

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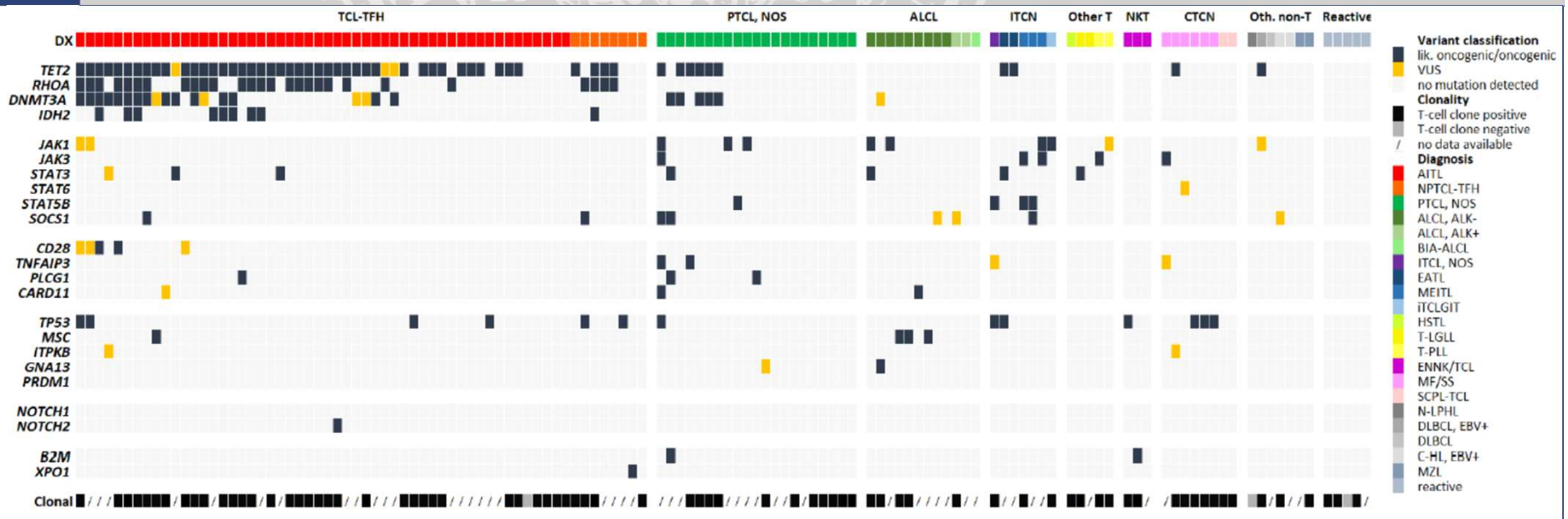
Targeted panel sequencing in the routine diagnosis of mature T- and NK-cell lymphomas: report of 128 cases from two German reference centers

Julia Böck[1], Katja Maurus[1], Elena Gerhard-Hartmann[1], Stephanie Brändlein[1], Katrin S. Kurz[2], German Ott[2], Ioannis Anagnostopoulos[1], Andreas Rosenwald[1] and Alberto Zamò[1]*



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frontiers | Frontiers in Oncology

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WHO-HAEM revised 4th edition	WHO-HAEM 5th edition 2022	ICC 2022
Peripheral T-cell lymphoma, not other specified	Peripheral T-cell lymphoma, not other specified	Peripheral T-cell lymphoma, not other specified
Variant of PTCL, NOS	EBV-positive nodal T- and NK-cell lymphoma	Primary nodal EBV-positive T-/NK-cell lymphoma (provisional entity)

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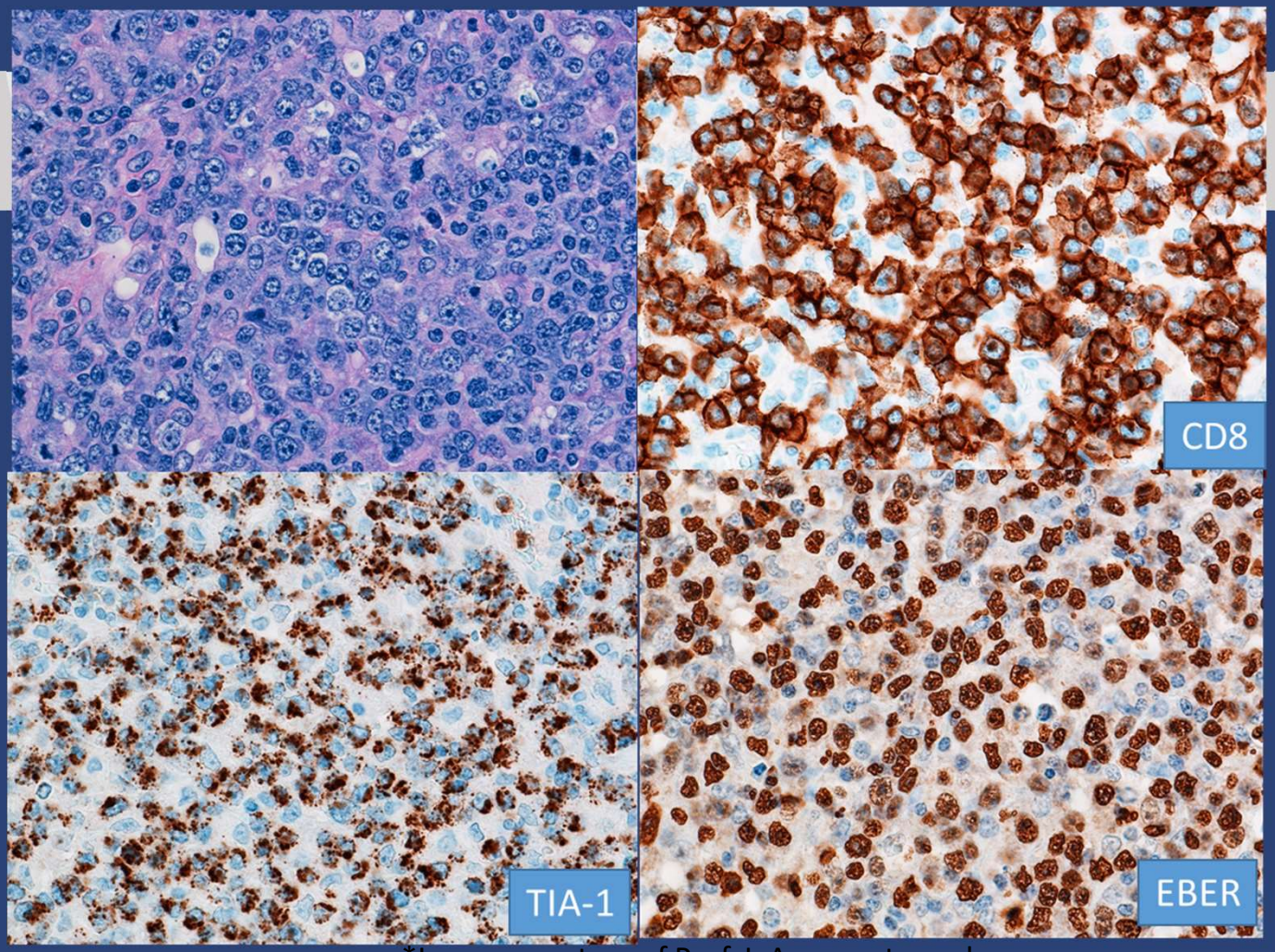

*Image: courtesy of Prof. I. Anagnostopoulos

WHO-HAEM 4th revised edition 2016	WHO-HAEM 5th edition 2022	ICC 2022
Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma*	Extranodal NK/T-cell lymphoma, **nasal type**

*la specificazione „nasal type“ viene omessa nella WHO-5 per sottolineare la frequente localizzazione extra-nasale

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WHO-HAEM 4th edition	WHO-HAEM 5th edition 2022	ICC 2022
Indolent T-cell **lymphoproliferative disorder** of the gastrointestinal tract	**Indolent T-cell lymphoma of the gastrointestinal tract**	Indolent **clonal** T-cell **lymphoproliferative disorder** of the gastrointestinal tract
-	Indolent **NK-cell** lymphoproliferative disorder of the gastrointestinal tract	Indolent **NK-cell** lymphoproliferative disorder of the gastrointestinal tract
Enteropathy-associated T-cell lymphoma - Refractory coeliac disease (RCD) Type I - RCD Type II	Enteropathy-associated T-cell lymphoma - RCD Type I - RCD Type II	Enteropathy-associated T-cell lymphoma **Type II refractory coeliac disease**
Monomorphic epitheliotropic intestinal T-cell lymphoma	Monomorphic epitheliotropic intestinal T-cell lymphoma	Monomorphic epitheliotropic intestinal T-cell lymphoma
Intestinal T-cell lymphoma, NOS	Intestinal T-cell lymphoma, NOS	Intestinal T-cell lymphoma, NOS

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Classificazioni WHO e ICC delle neoplasie T

- Mostrano discrepanze minori
- I linfomi nodali che esprimono molecole caratteristiche di T-FH sono raggruppati insieme. Presentano un immunofenotipo comune e frequenti mutazioni di TET2, DNMT3A, RHOA e IDH2
- L'analisi delle mutazioni è utile nella diagnosi dei linfomi T
- Entità indolenti: processo LP/linfoma T indolente del tratto GI e processo LP/linfoma NK indolente del tratto GI

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Conclusioni

- Precisione dei criteri diagnostici con inclusione della genetica
- Attenzione a forme pseudo-aggressive, specie nella popolazione pediatrica o giovani adulti
- WHO e ICC sono molto simili, la WHO propone più cambiamenti nella nomanclatura (eccezione: MM, N-LPHL)

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