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S.C. Anatomia e Istologia Patologica

WHO 5°ed vs ICC «survival guide» : neoplasie linfoidi

Savona 13-11-2024

Dott. Giulio Fraternali Orcioni

Conflitti di interesse

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]

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

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

WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Pre-neoplastic and neoplastic small lymphocytic proliferations		
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
Splenic B-cell lymphoma and leukemias		
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)
Lymphoplasmacytic lymphoma and IgM MGUS		
Lymphoplasmacytic lymphoma	Lymphoplasmacytic lymphoma	Lymphoplasmacytic lymphoma
	- IgM-LPL/Waldenstrom macroglobulinemia	
	- non-IgM-LPL/Waldenstrom macroglobulinemia	
IgM MGUS	IgM MGUS (see plasma cell neoplasms)	IgM MGUS
		- Plasma cell type
		- Not otherwise specified (NOS)
Not considered as an entity	Cold agglutinin disease (new entity, not included in this category; see plasma cell neoplasms)	Cold agglutinin disease (new entity)
Marginal zone lymphoma		
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

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

B-cell lymphomas with prevalent spleen involvement

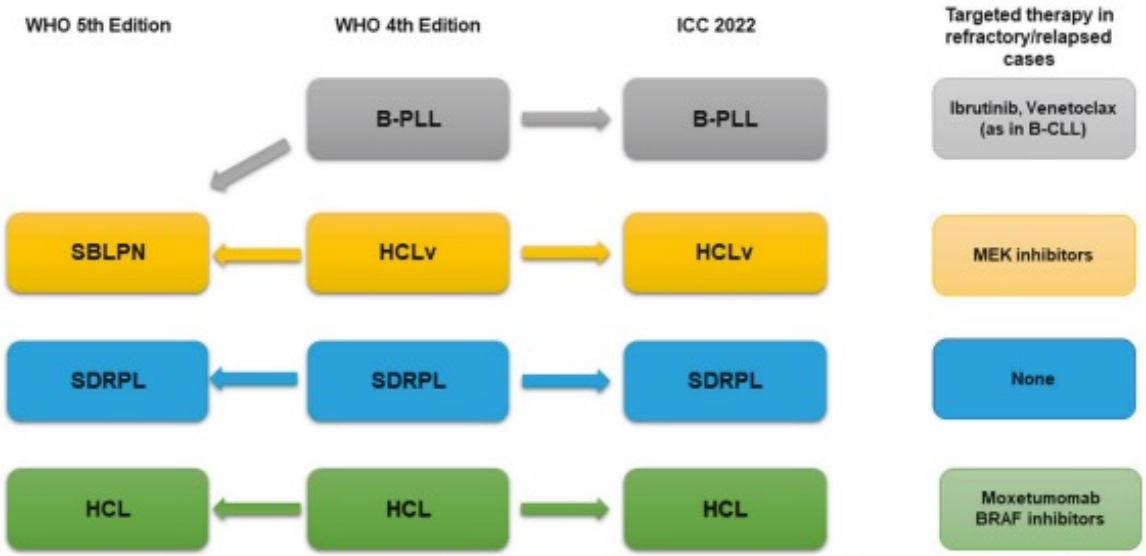
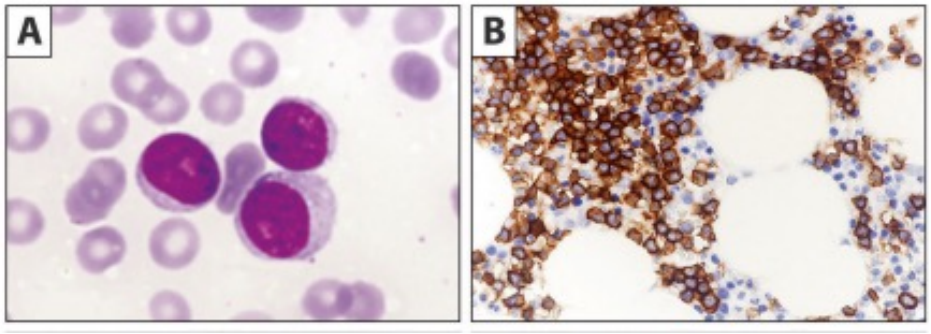


Fig. 2 Relationship between different types of B-cell lymphomas with prevalent spleen involvement among the ICC and WHO classifications. B-cell prolymphocytic leukemia (B-PLL), a definite entity in ICC, and hairy cell leukemia variant (HCLv), a provisional entity in ICC, are named in the WHO-HAEM5 under the term of splenic B-cell lymphoma with prominent nucleoli (SBLPN). SBLPN is an heterogeneous category that also comprises cases of unrecognized leukemic mantle cell lymphoma and progressed B-CLL. SDRPL splenic diffuse red pulp small B-cell lymphoma, HCL hairy cell leukemia, SMZL splenic marginal zone lymphoma.

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

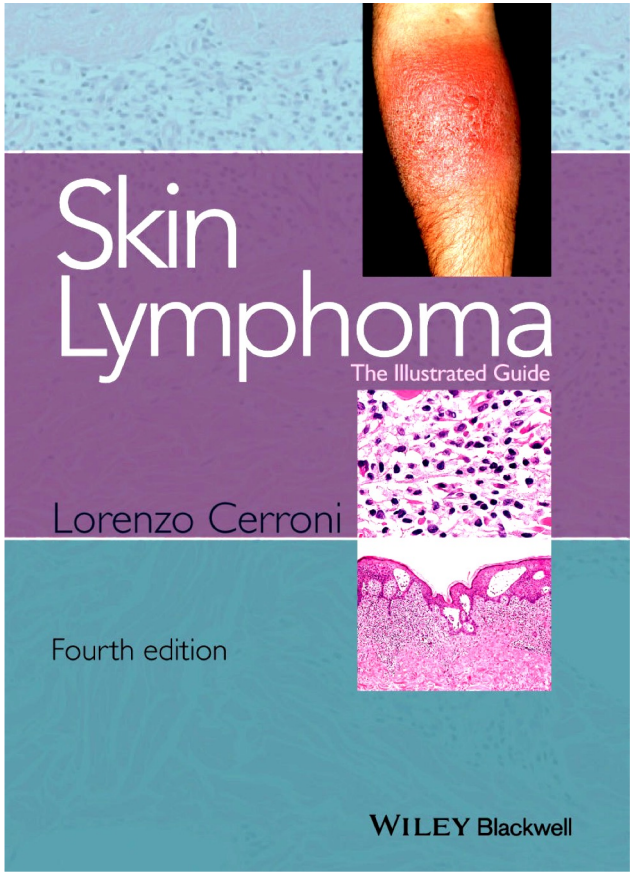
B-cell prolymphocytic leukaemia (B-PLL) solo ICC



B-cell prolymphocytic leukemia (B-PLL)

"B-cell prolymphocytic leukemia (B-PLL)" usually occurs in older patients and is characterized by high leukocyte count with >55% prolymphocytes (Fig. 1A), splenomegaly, minimal/absent lymphadenopathy and aggressive course. In the WHO-HAEM5, B-PLL has been deleted as an entity being regarded as a heterogeneous category including cases of hairy cell leukemia variant (HCLv), leukemic mantle cell lymphoma (MCL) and CLL/SLL progressed to B-PLL. Thus, now it has been in part absorbed in the new entity named "splenic B-cell leukemia with prominent nucleoli" (SBLPN) that also includes HCLv (Table 1 and Fig. 2). Conversely, the ICC still regards B-PLL as an entity but recommends its diagnosis only in cases without previous history of B-CLL (to exclude CLL progressing to B-PLL), negative for cyclin D1 and SOX11 (to exclude MCL), and lacking hairy surface projections and intrasinusoidal bone marrow (BM) infiltration (to exclude HCLv and splenic marginal zone lymphoma (SMZL)) (Fig. 1B). B-PLL usually carries a complex karyotype with rearrangement and/or increased copy number of *MYC* (62%), del17p (38%) and trisomy 18 (30%) [17]. B-PLL patients are treated according to B-CLL guidelines. B-PLL harboring *TP53* mutations and/or deletions that predict poor survival usually benefit from bruton tyrosine kinase inhibitors (BTKi) [18, 19]. Patients failing BTKi may still respond to the BCL2 inhibitor venetoclax [20].

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

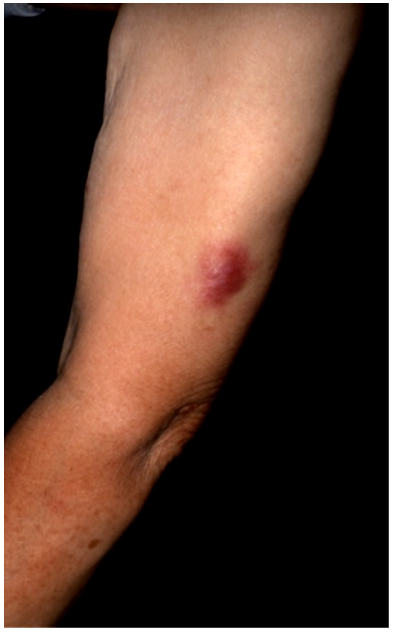


Cutaneous marginal zone lymphoma

1 **conventional variant 82%**

2 **lymphoplasmacytic variant 13%**

(c.d. cutaneous immunocytoma)



Solitary erythematous tumor on the arm

Résumé

Cutaneous marginal zone lymphoma, conventional variant

Clinical	Young adults and adults; can occur in children. Solitary or grouped papules or small nodules. Preferential locations: upper extremities, trunk.	
Morphology	Patchy, nodular or diffuse infiltrates. Characteristic pattern with central nodular dark area composed of small reactive lymphocytes with or without the formation of germinal centers, surrounded by a pale area where neoplastic marginal zone cells, lymphoplasmacytoid cells, and plasma cells predominate.	
Immunology	CD20, 79a	+
	Bcl-2	+
	IRTA1	+
	CD5, 10, Bcl-6	–
	clg	+ (monoclonal)
Genetics	Monoclonal rearrangement of the Ig genes detected in 50–60% of cases. t(14;18)(q32;q21) in a minority of cases.	
Treatment guidelines	Excision of solitary lesions; rituximab; radiotherapy; "watchful waiting." Antibiotic treatment should be used as first-line treatment in cases with evidence of *B. burgdorferi* infection. Systemic chemotherapy reserved for patients with extracutaneous spread.	

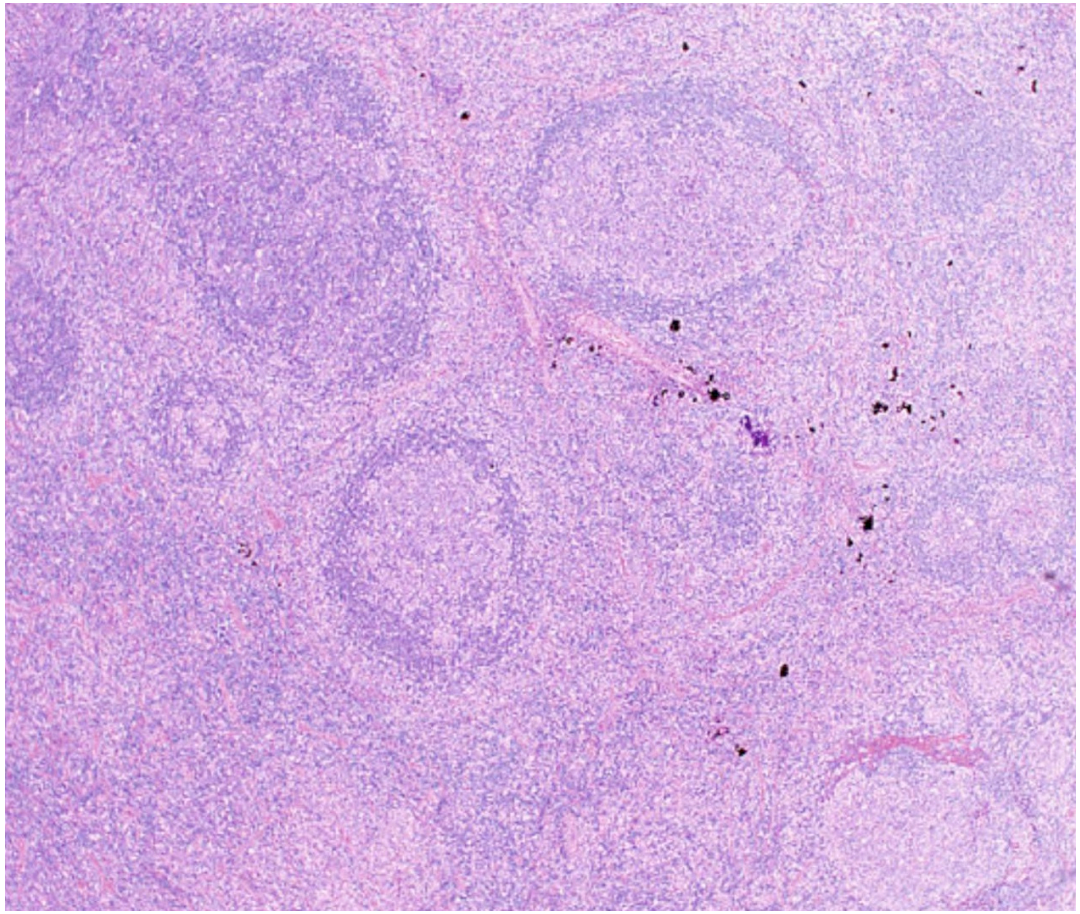
Marginal zone lymphomas

There is no indication for separately classifying extranodal MZLs of mucosa-associated lymphoid tissue (MALT lymphoma) based on site of presentation except for cutaneous MZL, which is now designated separately as a lymphoproliferative disorder (see "Cutaneous lymphomas" below). The clinical management approach, however, may differ between anatomic sites (eg, gastric MALT). In nodal MZL, significant heterogeneity is recognized, but there is no consensus on further alterations to the diagnostic criteria. The diagnosis of large-cell transformation of MZL should continue to rest on the finding of diffuse sheets of large cells.

from other MALT lymphomas. They will now be called "primary cutaneous marginal zone LPD" rather than "lymphoma" because of their extremely indolent behavior; disease-specific survivals approach 100% without requiring aggressive therapies. However, cutaneous recurrences are common. Primary cutaneous marginal zone LPDs show significant differences compared with MALT lymphomas at other sites.[7,279-285] Two subtypes of this disorder are

Linfoma marginale (nodale) di tipo pediatrico

- WHO 5°ed : entità distinta
- ICC : entità provvisoria di cui viene sottolineata la convergenza con LNH follicolare di tipo pediatrico avendo mutazioni simili es. TNFRFS14, IRF8, MAP2KI
- DD : iperplasia follicolare atipica da H. influenzae



WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Follicular lymphoma		
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)
Mantle cell lymphoma		
In situ mantle cell neoplasia	In situ mantle cell neoplasm	In situ mantle cell neoplasia
Mantle cell lymphoma	Mantle cell lymphoma	Mantle cell lymphoma
Leukemic non-nodal mantle cell lymphoma	Leukemic non-nodal mantle cell lymphoma	Leukemic non-nodal mantle cell lymphoma
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)

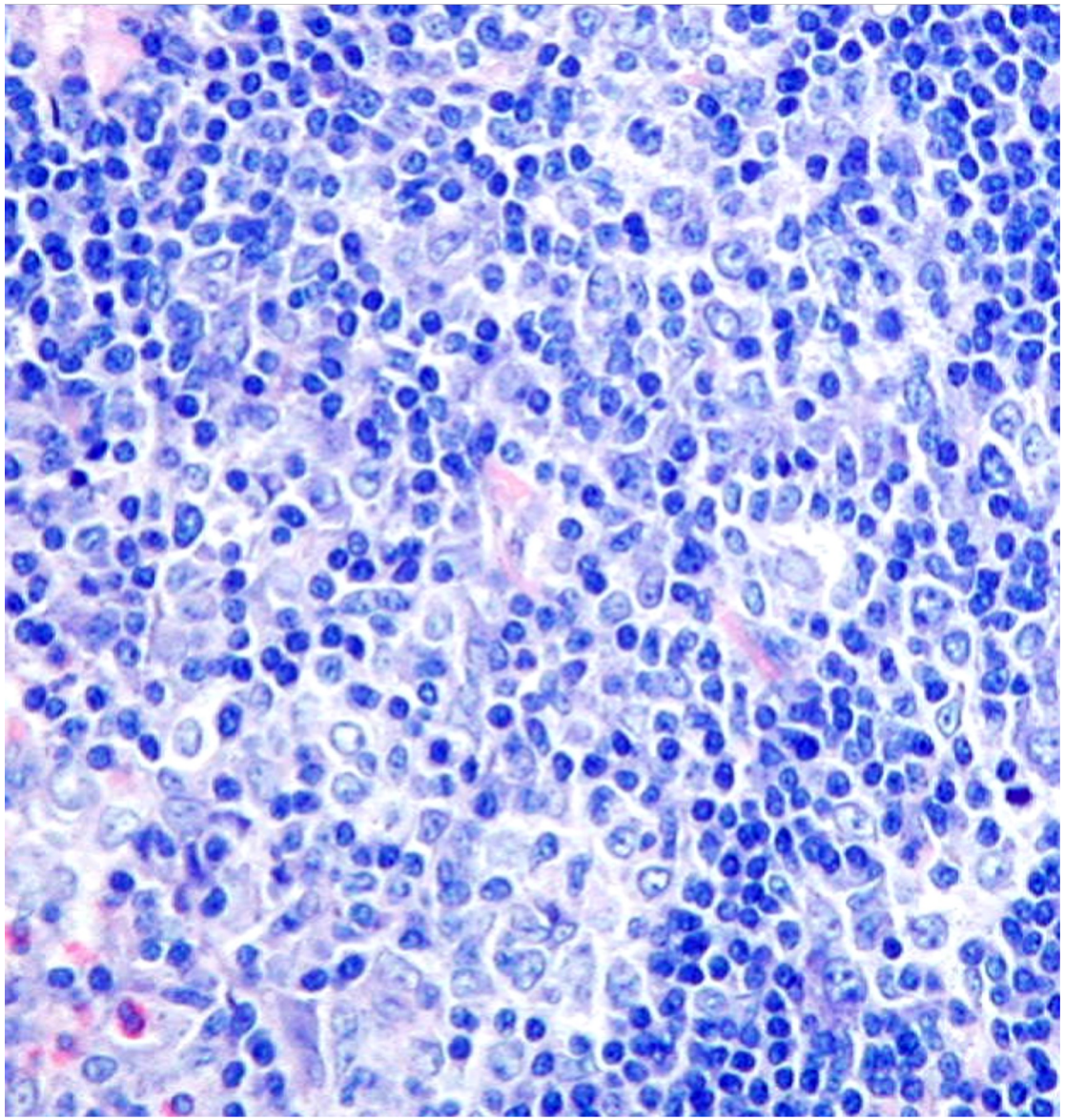
Leukemia (2023) 37:18–34; https://doi.org/10.1038/s41375-022-01764-1

Linfoma follicolare

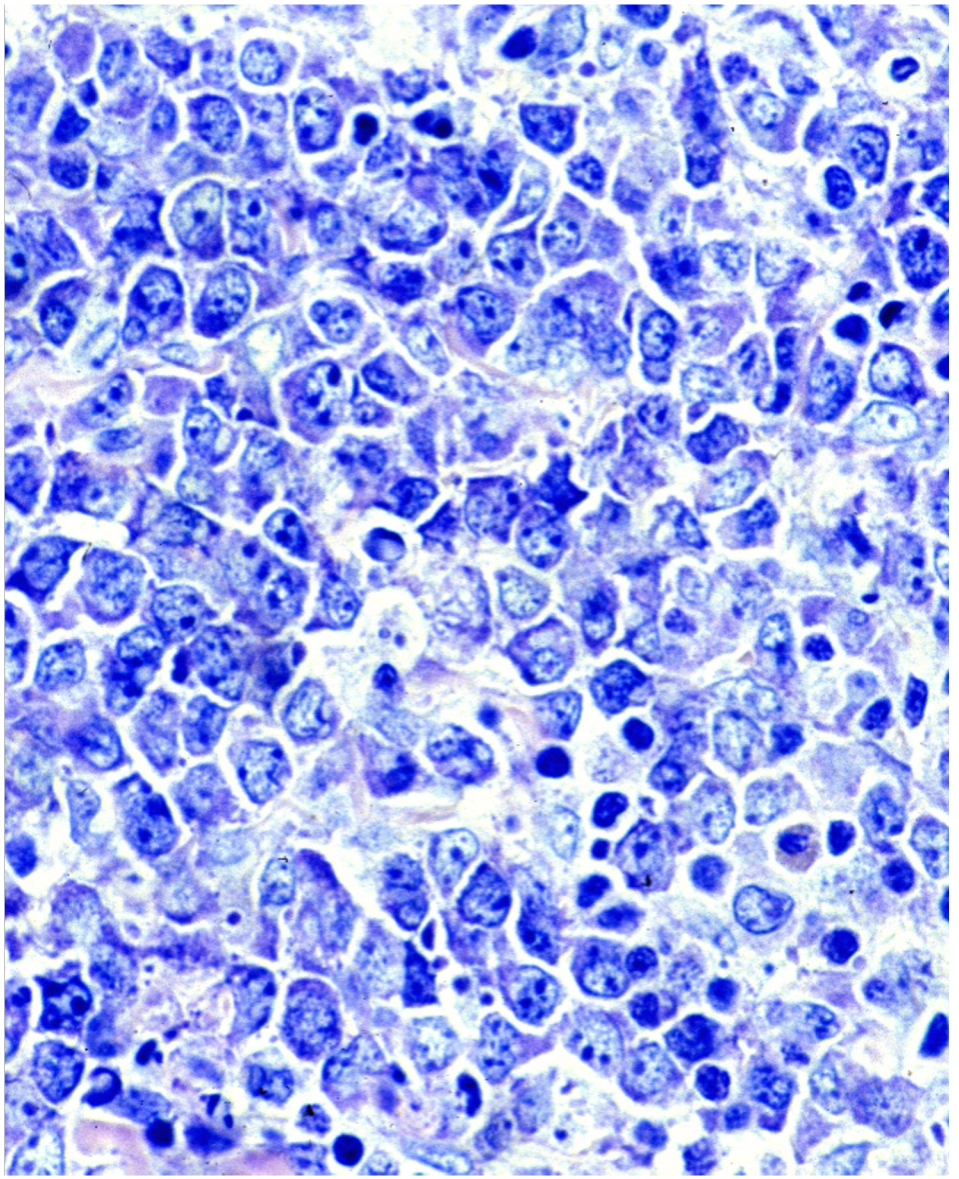
WHO-5

- Non necessario grading
- Linfoma follicolare a grandi cellule(FL 3B)
- FL3A diffuso non è considerato DLCBL
- Linfoma follicolare «classico»
- Linfoma follicolare «non convenzionale»

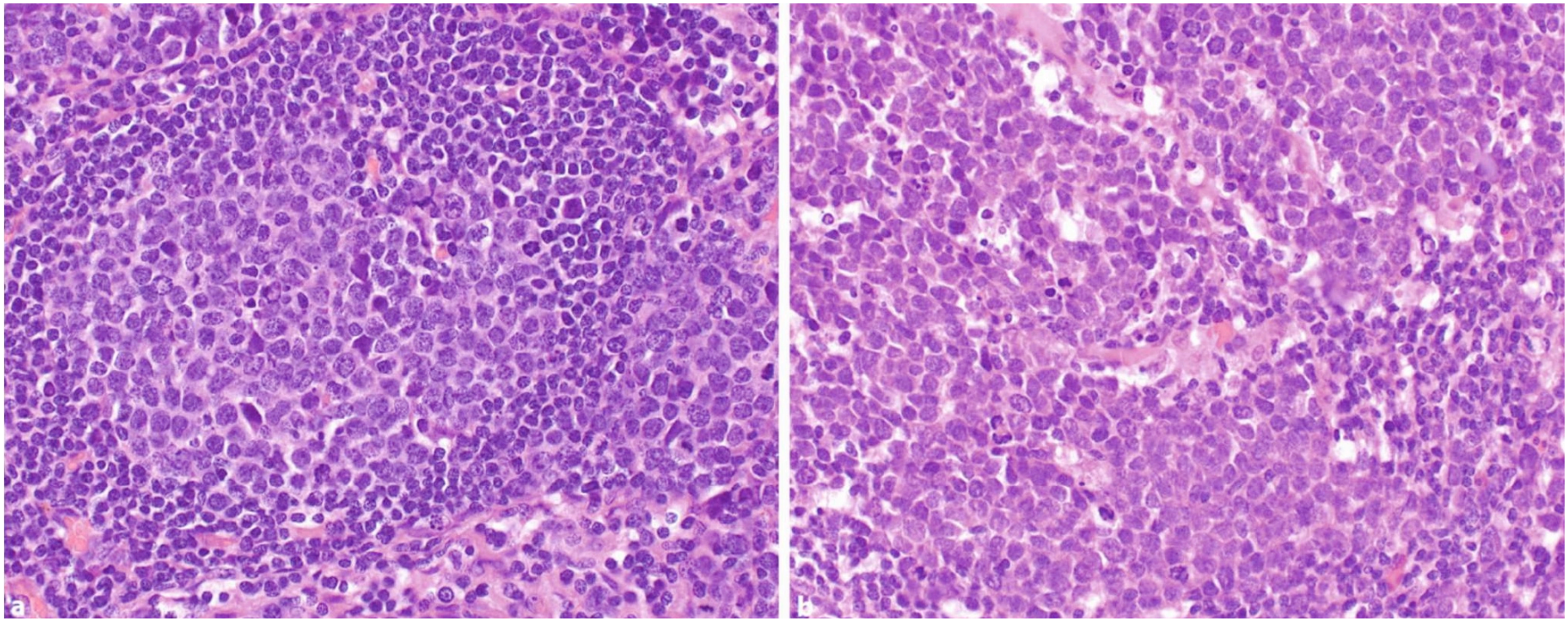
Grado IIIa (> 15 Cb/HPF)



Grado IIIb (solo Cb)



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



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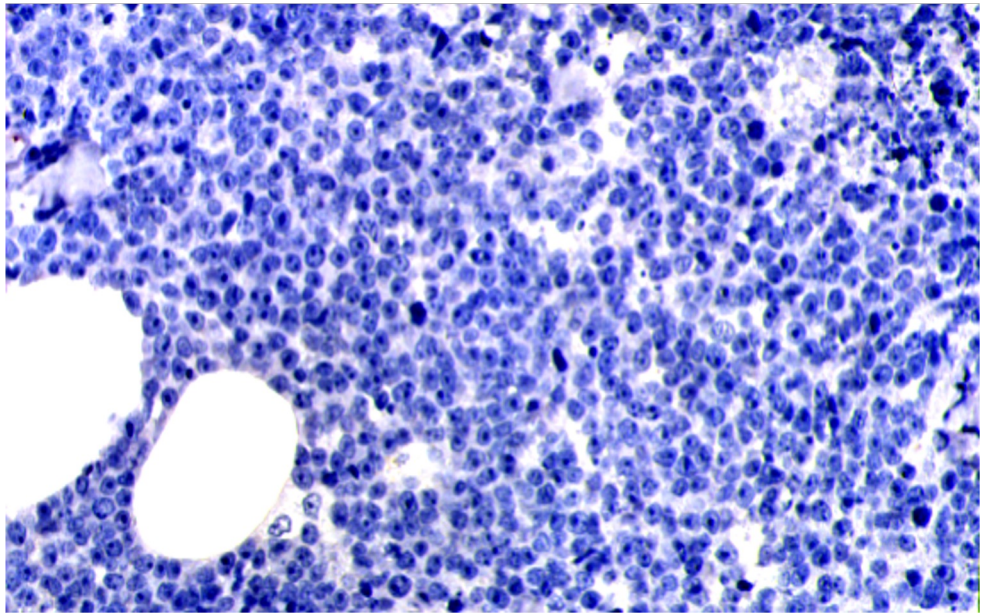
Linfoma follicolare non convenzionale (WHO 5 ed)

Varietà blastoide

Natkunam Y et al. Am J Surg Pathol 2000; 24:525-534.

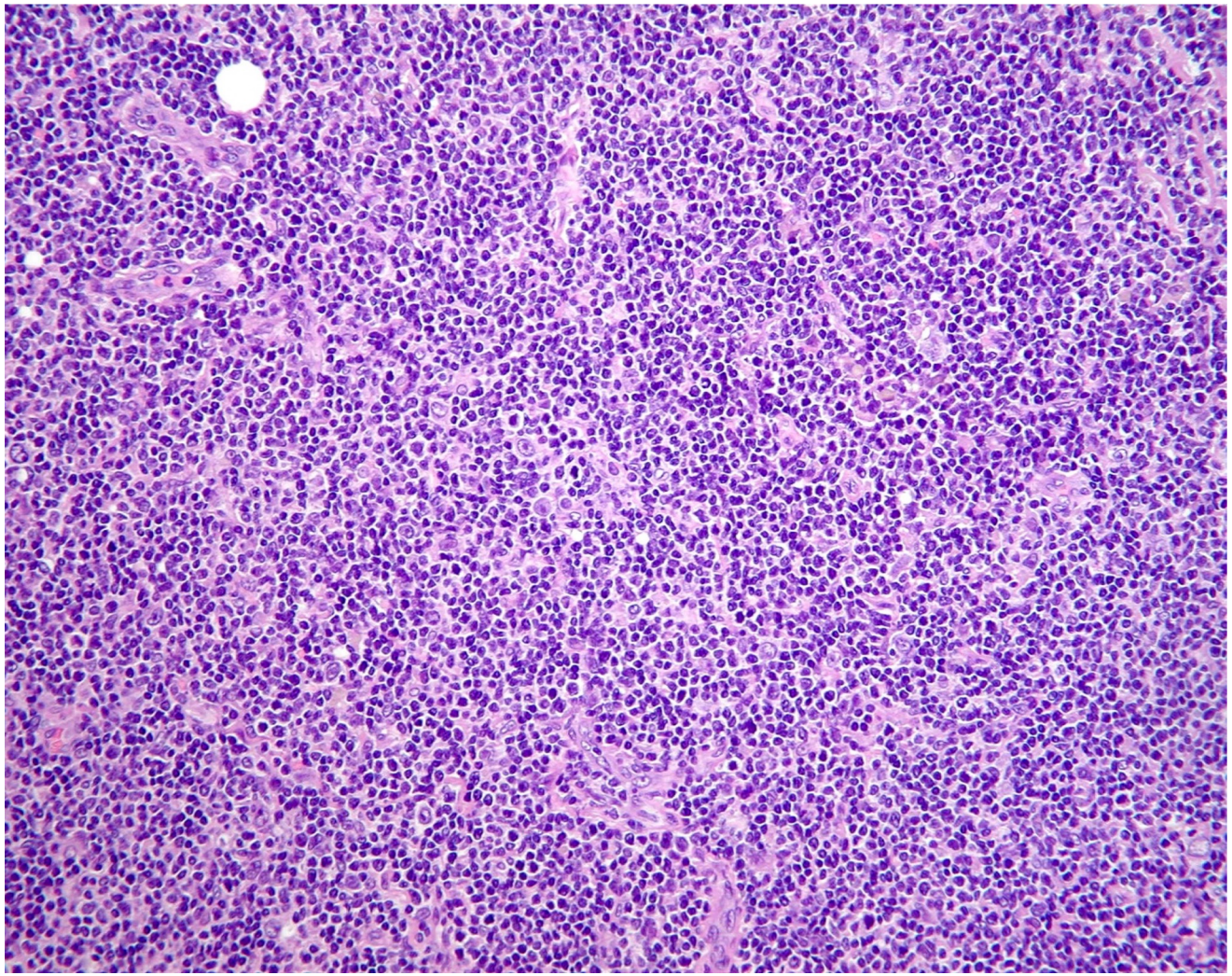
- Espressione del prodotto di C-myc, secondaria a riarrangiamento del gene *MYC, e* conseguente aspetto linfoblastoide.



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

Linfoma follicolare non convenzionale (WHO 5 ed)

LNH follicolare con pattern di crescita prevalentemente diffuso (< 5% casi)



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]

[1]Department of Pathology, University of Würzburg, Würzburg; [2]Department of Clinical Pathology, Robert-Bosch-Krankenhaus, Stuttgart; [3]Clinic for Internal Medicine III, University Hospital of Ulm, Ulm; and [4]Department of Pathology, Caritas-Krankenhaus, Bad Mergentheim, Germany

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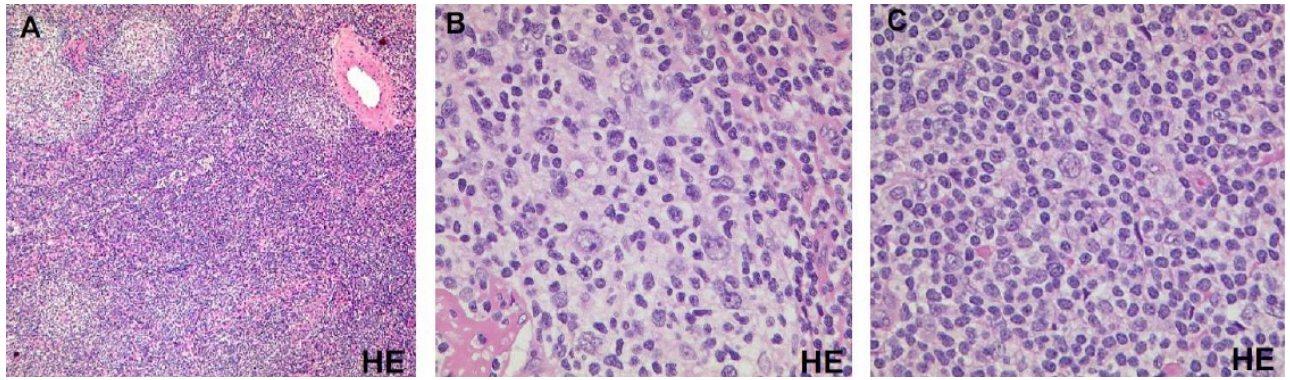
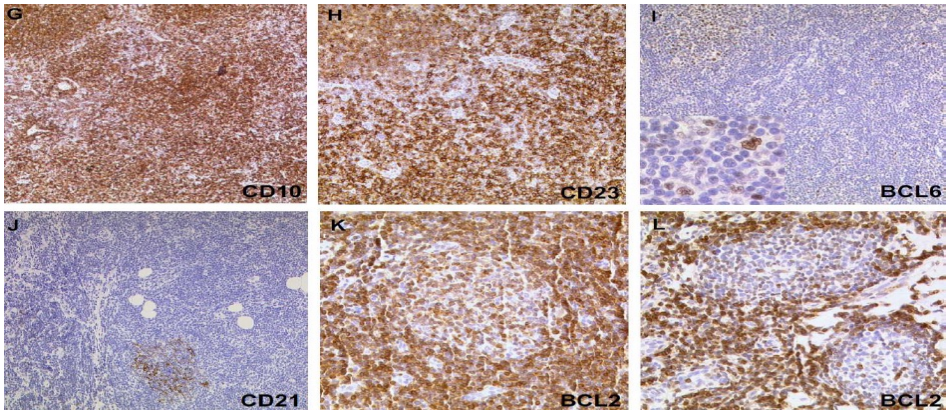
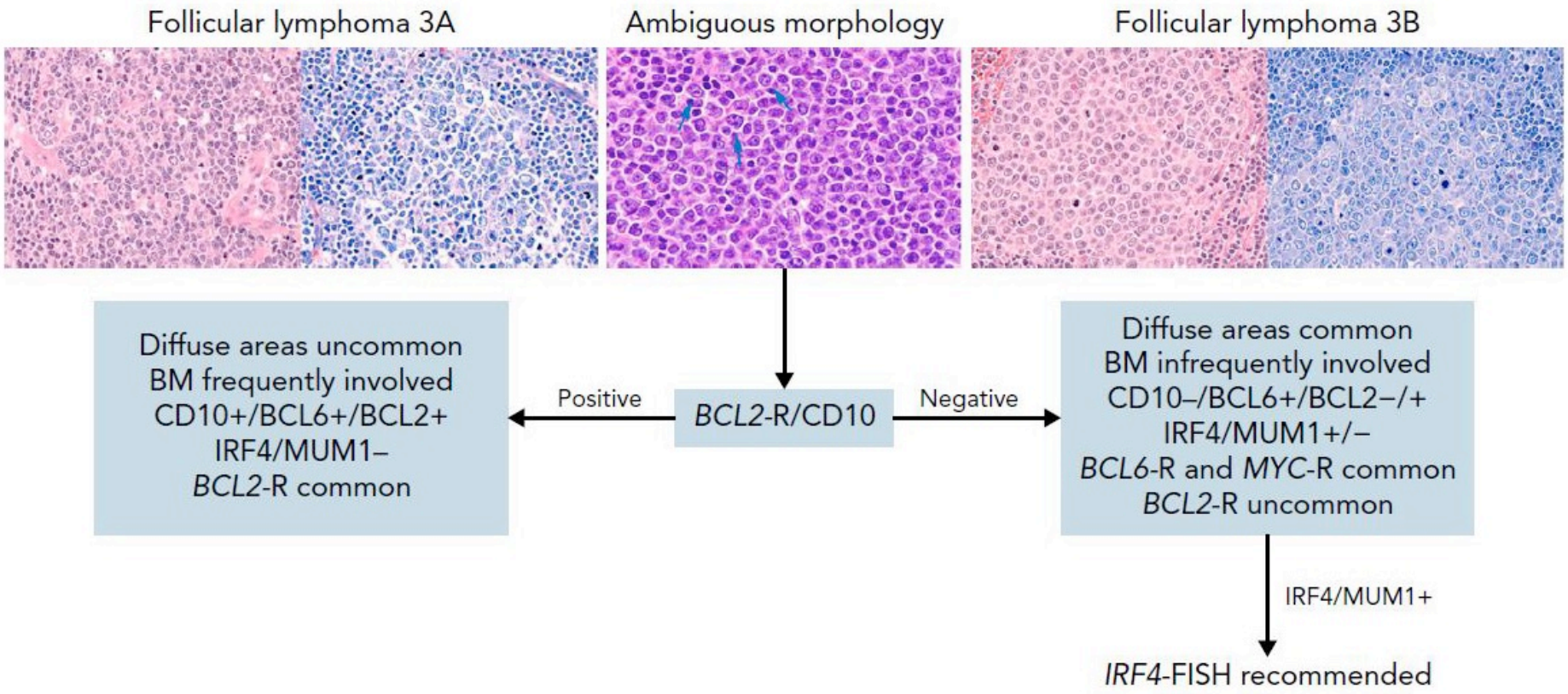


- Frequentemente inguinale, stadio I-II
- Morf e IHC caratteristiche
- > 80 % mutazioni di STAT-6 e CREBBP





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**

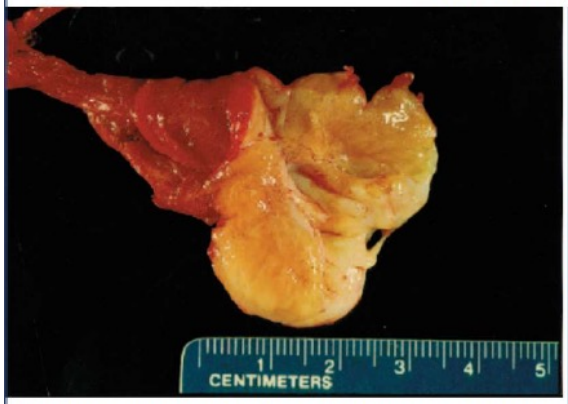


FIGURE 1. Gross photograph of the left testicle removed by left radical orchiectomy. Cut surface shows a homogeneous tan surface without necrosis and hemorrhage.

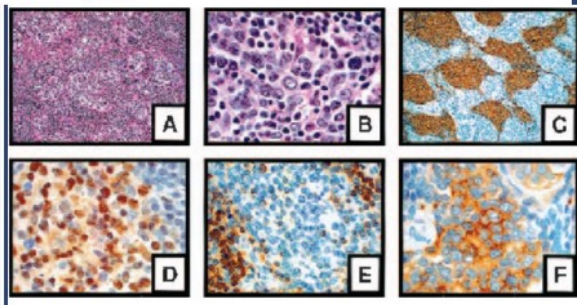


FIGURE 2. Microscopic sections showed a dense lymphoic infiltrate with a vague nodular growth pattern infiltrating sem iniferous tubules (**A**, 10× magnification), with large lymphoic cells having open chromatin and distinct nucleoli (**B**, 40×) Tumor cells were positive for CD20 (**C**), BCL6 (**D**), and CD1((**F**) but negative for BCL2 (**E**), diagnostic of follicular lym phoma, grade 3 of 3.

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

- Paz prev. pediatrici
- Stadio IE
- LDH normale o l.a.
- Curabile con orchiect +/- RT +/- CT
- 3A, possibili aree diffuse, fen GCB
- t(14;18) neg
- Frequenti mutazioni di TNFRSF14 e MAP2K1
- DD : DLBCL testis (ABC, MYD88 neg, BCL-2 ++).

Pediatric-type FL remains a clearly defined entity with recurrent genomic alterations and excellent prognosis with conservative management.[80-83] Distinguishing pediatric-type FL from FL grade 3B remains critical. Recent work has suggested that pediatric-type FL may be related to the pediatric variant of MZL, which had been listed as provisional in the classification.[84] Testicular FL, recognized as a new distinct entity of FL in young boys, shares pathological and clinical features with pediatric-type FL, because most patients can be managed conservatively, without systemic chemotherapy.[85,86]

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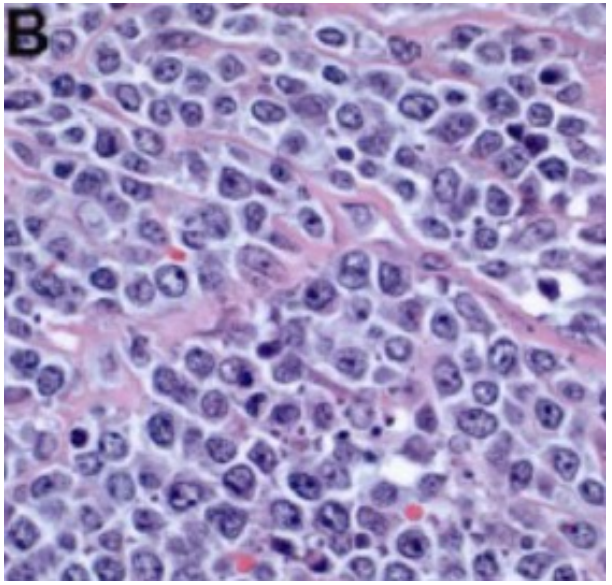
https://doi.org/10.1007/s00428-023-03590-x

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]

Large B-cell lymphoma with *IRF4* rearrangement, upgraded now to a definite entity, is most common in children and young adults and usually has at least a partially follicular growth pattern.[69] However, the same disease is not commonly seen in adults. FISH for *IRF4*-R must be performed for diagnosis. Patients lacking demonstrable rearrangements should have evidence of either IGH or IGK/IGL breaks. Detection of *IRF4* mutation may support the diagnosis.[69] *IRF4*-R can occur in other aggressive B-cell lymphomas associated with *BCL2*-R or *MYC*-R, mainly in adults, and in this context, it is not specific for the entity.[69]



- Giovani adulti
- Prevalentemente cervicale e anello del Waldeyer, stadio I-II
- Morfologia FL 3A/3B +/- DLBCL
- IHC : 80 % triplo positivo (CD10 +, bcl-6+, MUM1/IRF4+), spesso CD5 +.

High grade (WHO-5)/Large cell lymphoma (ICC) with 11q aberrations

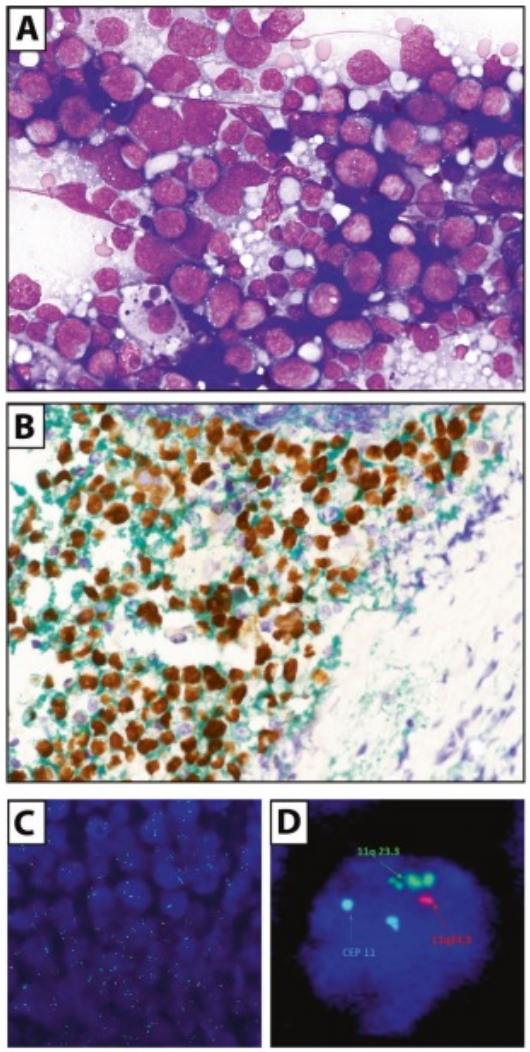


Fig. 3 DLBCL/HGBCL with 11q rearrangements. A Lymph node imprint showing large-size tumor cells with basophilic cytoplasm and round nuclei with evident nucleoli (May-Grunwald-Giemsa; ×400). **B** Tumor cells are double stained for CD20 (green) and BCL6 (brown). **C**, **D** FISH reveals 11q aberrations.

- Prevalentemente giovani, possibile anche in anziani
- Morfologia variabile (spesso Burkitt-simile)
- Immunofenotipo Burkitt-simile
- MYC-R negativo
- 11q23gain + 11q24 loss
- Mutazioni più simili a DLBCL (50 % GNA13)

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
Plasma cell neoplasms and other diseases with paraproteins		
	Monoclonal gammopathies	
IgM MGUS (Not included in this category; see lymphoplasmacytic lymphoma and IgM MGUS)	IgM MGUS	IgM MGUS (Not included in this category; see lymphoplasmacytic lymphoma and IgM MGUS)
Non-IgM MGUS	Non-IgM MGUS	Non-IgM MGUS
Not considered as an entity	Cold agglutinin disease (see lymphoplasmacytic lymphoma)	Cold agglutinin disease (Not included in this category; see lymphoplasmacytic lymphoma)
Not considered as an entity	Monoclonal gammopathy of renal significant	Not considered as an entity
Heavy chain disease	Heavy chain disease	Heavy chain disease
- Mu heavy chain disease	- Mu heavy chain disease	- Mu heavy chain disease
- Gamma heavy chain disease	- Gamma heavy chain disease	- Gamma heavy chain disease
- Alpha heavy chain disease	- Alpha heavy chain disease	- Alpha heavy chain disease
Plasma cell myeloma	Plasma cell myeloma/Multiple myeloma	Multiple myeloma (plasma cell myeloma)
- Not considered as an entity	- Not considered as an entity	- Multiple myeloma, NOS
- Not considered as an entity	- Not considered as an entity	- Multiple Myeloma with recurrent cytogenetic abnormality
- Not considered as an entity	- Not considered as an entity	- Multiple myeloma with CCND family translocation
- Not considered as an entity	- Not considered as an entity	- Multiple myeloma with MAF family translocation
- Not considered as an entity	- Not considered as an entity	- Multiple myeloma with NSD2 translocation
- Not considered as an entity	- Not considered as an entity	- Multiple myeloma with hyperdiploidy
Solitary plasmacytoma of bone	Plasmacytoma (solitary plasmacytoma of bone, extraosseous plasmacytoma)	Solitary plasmacytoma of bone
Extraosseous plasmacytoma		Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition disease	Disease with monoclonal immunoglobulin deposition	Monoclonal immunoglobulin deposition disease
- Primary amyloidosis	- Immunoglobulin-related (AL) amyloidosis	- Ig light chain amyloidosis (AL)
- Not considered	- Not considered	- Localized AL amyloidosis
- Light chain and heavy chain deposition disease	- Monoclonal immunoglobulin deposition disease	- Light chain and heavy chain deposition disease
Plasma cell neoplasms with associated paraneoplastic syndrome	Plasma cell neoplasm with associated paraneoplastic syndrome	Plasma cell neoplasms with associated paraneoplastic syndrome
- POEMS syndrome	- POEMS syndrome	- POEMS syndrome
- TEMPI syndrome (provisional entity)	- TEMPI syndrome (upgraded to distinct entity)	- TEMPI syndrome
- Not considered as an entity	- AESOP syndrome (new entity)	- Not considered as an entity

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

Clinicians participating in the CAC strongly supported the term "multiple myeloma" over "plasma cell myeloma." MM is a genetically heterogeneous disease with 2 main groups defined by cytogenetics. Specifically, 40% to 50% of patients show recurrent IGH translocations with a variety of partner genes, whereas up to 55% of patients with MM lack IGH translocations and are characterized by hyperdiploidy, with a small subset of patients not falling into either category.[41,42] These primary genetic abnormalities are present in precursor conditions and persist throughout the disease course. They are associated with prognosis, treatment response, and other clinical and phenotypic features and have a strong correlation with the gene expression profile (GEP).[41,43-45] Therefore, MM can be formally divided into mutually exclusive diagnostic groups: (1) MM, NOS and (2) MM with recurrent genetic abnormalities, including MM with *CCND* family translocations, MM with *MAF* family translocation, MM with *NSD2* translocation, and MM with hyperdiploidy. Detection of t(4;14), t(14;16), and secondary changes, including del(17p), amp1q, and del(1p) identifies patients with high-risk disease.[46-48] Currently, interphase FISH is the tech-

Solitary plasmacytomas of bone and primary extramedullary plasmacytomas are plasma cell neoplasms with low to moderate risk for progression to MM.[56,57] Because minimal marrow involvement detected by flow cytometry (ie, clonal plasma cells present but <10%) is of major prognostic importance, particularly with solitary plasmacytomas of bone, this feature should be incorporated into the diagnosis of these entities.[56,58]

WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation		
Post-transplant	Post-transplant, HIV, Iatrogenic/autoimmune, inborn errors of immunity	Post-transplant
Non-destructive forms distincted in:	Hyperplasia arising in immune deficiency/ dysregulation distincted in:	Non-destructive forms distincted in:
- Plasmacytic hyperplasia	- Plasma-cell hyperplasia	- Plasmacytic hyperplasia
- Infectious mononucleosis	- Mononucleosis-like hyperplasia	- Infectious mononucleosis
- Florid follicular hyperplasia	- Follicular hyperplasia	- Florid follicular hyperplasia
Multicentric Castleman disease (not included in this category; see HHV8-associated-lymphoproliferative disorders)	KSHV/HHV8 Multicentric Castleman disease (also included in tumor-like lesion with B cell predominance)	Multicentric Castleman disease (not included in this category; see HHV8-associated-lymphoproliferative disorders)
Polymorphic	Polymorphic LPD arising in immune deficiency/ dysregulation	Polymorphic
Epstein-Barr virus-positive mucocutaneous ulcer (not included in this category; see large B-cell lymphoma)	Epstein-Barr virus-positive mucocutaneous ulcer	Epstein-Barr virus-positive mucocutaneous ulcer (not included in this category; see large B-cell lymphoma)
Monomorphic B and T cell neoplasms, cHL	Lymphomas arising in immune deficiency/ dysregulation	Monomorphic B and T cell neoplasms, cHL
Lymphomas associated with HIV infection		
Other iatrogenic immunodeficiency-associated LPDs		Other iatrogenic immunodeficiency-associated LPDs
Lymphoproliferative disease associated with primary immune disorders	In born error of immunity-associated lymphoid proliferations and lymphomas	

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WHO Classification, revised 4th edition	WHO Classification, 5th edition	ICC 2022
KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas		
Multicentric Castleman disease	KSHV/HHV8 Multicentric Castleman disease (Not included in this category; see lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation)	Multicentric Castleman disease
HHV8-positive germinotropic lymphoproliferative disorder	KSHV/HHV8-positive germinotropic lymphoproliferative disorder	HHV8-positive germinotropic lymphoproliferative disorder
HHV8-positive diffuse large B-cell lymphoma, NOS	KSHV/HHV8-positive diffuse large B-cell lymphoma	HHV8-positive diffuse large B-cell lymphoma, NOS
Primary effusion lymphoma	Primary effusion lymphoma	Primary effusion lymphoma
Burkitt lymphoma		
Burkitt lymphoma	Burkitt lymphoma (emphasis is given in distinguishing EBV+ and EBV- cases)	Burkitt lymphoma
Hodgkin lymphoma		
Classic Hodgkin lymphoma	Classic Hodgkin lymphoma (subtypes maintained as in 4th WHO edition)	Classic Hodgkin lymphoma (subtypes maintained as in 4th WHO edition)
Nodular lymphocyte predominant Hodgkin lymphoma	Nodular lymphocyte predominant Hodgkin lymphoma	Nodular lymphocyte predominant B-cell lymphoma (not included in this category; see large B-cell lymphomas)
Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation		
Post-transplant	Post-transplant, HIV, Iatrogenic/autoimmune, inborn errors of immunity	Post-transplant

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

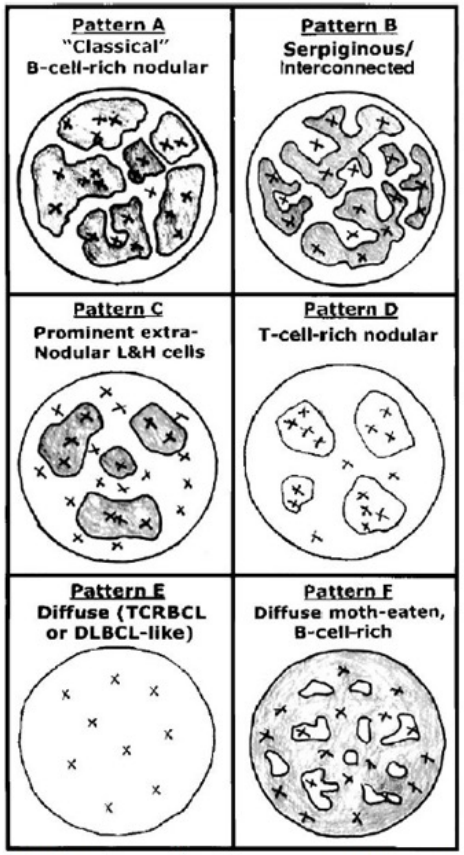

FIGURE 3. Immunoarchitectural patterns in NLPHL in schematic form (X: L&H cells, gray background; B-cell-rich background, blank/white background; T-cell-rich background). A, "Classic" B-cell-rich nodular pattern. B, Serpiginous nodular pattern. C, Nodular pattern with many extranodular L&H cells. D, T-cell-rich nodular pattern. E, Diffuse, T-cell-rich (TCRBCL-like) pattern. F, (Diffuse), moth-eaten (B-cell-rich) pattern.

(*Am J Surg Pathol* 2003;27:1346–1356)

The CAC conference discussed key issues related to the classification of Hodgkin lymphomas and patients with borderline diagnostic criteria. The conference concluded that new terminology is warranted for nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), based on major biological and clinical differences with CHL and with close relationship to T-cell/histiocyte-rich large B-cell lymphoma.[198] The term "nodular lymphocyte predominant B-cell lymphoma" (NLPBL) was accepted by consensus. The value of identifying variant histology in NLPBL was recognized, with the suggestion that typical patients with Fan patterns A, B, and C or grade 1 be distinguished from Fan patterns D, E, and F or grade 2.[199] Patients falling within grade 2 generally show loss of a well-formed nodular pattern and increased infiltration by T cells with a reduction of background small B cells. Patients with grade 2 histology may warrant treatment for DLBCL, but clinical features should play a role in treatment decisions.[200] Rare examples of NLPBL are EBV-positive with uncertain clinical implications.[201]

NLPHL (± THRLBCL-like areas) *versus* THRLBCL

1. **Tumor cell phenotype is almost identical**
   Incostant (and practically poorly applicable) differences in expression of markers such as LSP1, PU.1, FREB, MUM1, …

Molecular features in NLPHL and THRLBCL	
Similarities	**Differences**
• **Rearranged, mutated *IGH* genes with ongoing mutations** • **Frequent partial gain of 4q and losses of 19/19p**	• **BCL6 translocation (>> in NLPHL)** • **In NLPHL higher number of genomic imbalances** (average of 4.7 in THRLBCL versus 10.8 in NLPHL) and **distribution** (usually 1–5 in THRLBCL versus 6–22 in NLPHL)
GEP analysis show more similarities than differences between tumor cells in NLPHL and THRLBCL	

American Journal of Hematology, Vol. 90, No. 6, June 2015

RESEARCH ARTICLE

Incidence, management, and outcome of high-grade transformation of nodular lymphocyte predominant Hodgkin lymphoma: Long-term outcomes from a 30-year experience

Toby A. Eyre,[1]* Kevin Gatter,[2] Graham P. Collins,[1] Georgina W. Hall,[3] Caroline Watson,[1] and Chris S.R. Hatton[1]

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a rare form of Hodgkin lymphoma that typically presents as early stage, indolent disease in young adult males. The relationship between NLPHL and DLBCL is incompletely understood, and there remains a paucity of data with regard the incidence and management of high-grade transformation. We report the largest study to date describing the incidence, management and long-term outcome of 26 cases of high-grade transformation of NLPHL over a 30-year period. We report a transformation incidence of 17.0%. Bone marrow, splenic, and liver infiltration with DLBCL was frequent. Patients with an aa-IPI 2–3 have poorer OS and PFS ($P = 0.034$ and $P = 0.009$, respectively). Although the approach to treatment was somewhat variable, typically young, otherwise fit patients received anthracycline-based induction, platinum-based consolidation with stem cell harvesting, followed by autologous SCT with BEAM conditioning. Long-term (5 year) PFS was over 60% with this approach, and comparable to our de novo DLBCL historical age and time period-matched cohort largely treated with CHOP-like chemotherapy alone. The transformation rate of 17.0% highlights the importance of accurate initial diagnosis, long-term follow-up, and re-biopsy at relapse.

Am. J. Hematol. 90:E103–E110, 2015.

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Diffuse large B-cell lymphoma, NOS	The cell-of-origin designation in diffuse large B-cell lymphoma, NOS should be maintained, but it is considered insufficient to fully capture the biological complexity of these tumors. Molecular profiling studies have identified 5 to 7 new functional genetic subgroups of diffuse large B-cell lymphoma that may provide more precise patient stratification in the future.
Large B-cell lymphoma with 11q aberration	This term replaces Burkitt-like lymphoma with 11q aberration, and the entity is still considered provisional. Molecular studies indicate that it is closer to diffuse large B-cell lymphoma than to Burkitt lymphoma.
Nodular lymphocyte predominant B-cell lymphoma	This term replaces nodular lymphocyte-predominant Hodgkin lymphoma, recognizing major biological and clinical differences from classic Hodgkin lymphoma. Close relationship to T-cell/histiocyte-rich large B-cell lymphoma is emphasized.
Primary diffuse large B-cell lymphoma of the testis	Now recognized as a specific entity closely related to primary diffuse large B-cell lymphoma of the central nervous system. Most patients share molecular and cytogenetic features of the MCD/C5[131-134] subgroup of diffuse large B-cell lymphoma, similar to some other primary extranodal large B-cell lymphomas of the activated B-cell–like subtype.
HHV-8 and Epstein-Barr virus–negative primary effusion-based lymphoma	Recognized as a provisional entity frequently associated with fluid overload. Patients who conform to other well-defined lymphomas should not be included.
Epstein-Barr virus–positive mucocutaneous ulcer	Now recognized as a definite entity, and diagnostic criteria have been refined.
Epstein-Barr virus–positive diffuse large B-cell lymphoma, NOS	Tumors are morphologically heterogeneous, but the distinction between polymorphic and monomorphic does not have prognostic significance in the elderly. The T-cell/histiocyte-rich large B-cell lymphoma–like pattern, more common in younger patients (younger than age 45 years), is distinct from what has been termed polymorphic.
Lymphomatoid granulomatosis	Generally diagnosed in the absence of known immunodeficiency and, per definition, requires pulmonary involvement. Isolated central nervous system or gastrointestinal tract involvement by an Epstein-Barr virus–positive lesion resembling lymphomatoid granulomatosis is usually associated with immunodeficiency and Epstein-Barr virus latency III. These patients should be classified as Epstein-Barr virus–positive B-cell lymphoproliferative disorder or Epstein-Barr virus–positive diffuse large B-cell lymphoma, NOS and not as lymphomatoid granulomatosis.

HGBL NOS

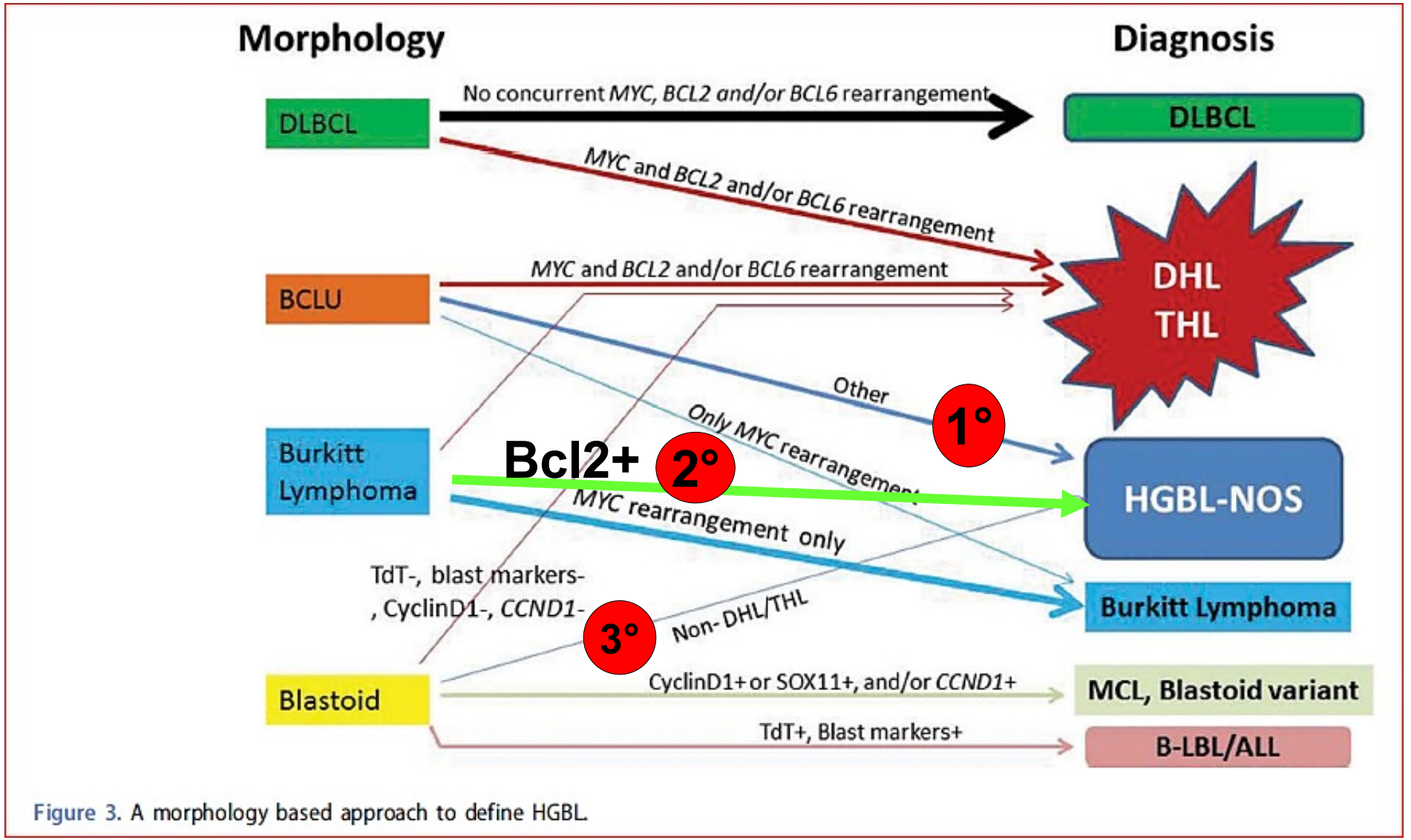

Figure 3. A morphology based approach to define HGBL.

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

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High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangement	The category is redefined to exclude patients with only *MYC* and *BCL6* rearrangements. Some neoplasms may express terminal deoxynucleotide transferase without being considered a B-lymphoblastic neoplasm.
High-grade B-cell lymphoma with MYC and BCL6 rearrangements	With the change in the definition of high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements, this provisional category was added.
Mediastinal gray-zone lymphoma	Criteria for distinction from classic Hodgkin lymphoma have been refined. Clinical and genomic data indicate that most non-mediastinal gray-zone lymphomas are distinct from mediastinal gray-zone lymphoma; thus, patients with extra-mediastinal disease should be diagnosed as having diffuse large B-cell lymphoma, NOS.

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

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ALK-negative anaplastic large cell lymphoma	*DUSP22*-R ALK anaplastic large cell lymphoma is now defined as a genetic subtype of systemic ALK-negative anaplastic large cell lymphoma. *JAK2* rearrangements or coexisting *TP63* and *DUSP22* rearrangements are rarely seen; understanding their significance requires further study.
Breast implant–associated anaplastic large cell lymphoma	Upgraded from a provisional to a definite entity. Use of tumor-node-metastasis staging criteria is recommended to facilitate clinical management.
Histiocytic and dendritic cell neoplasms	ALK-positive histiocytosis is accepted as an entity in the classification. A subset of Rosai-Dorfman-Destombes disease is identified as neoplastic based on clonal genetic alterations.
Epstein-Barr virus–positive inflammatory follicular dendritic cell/fibroblastic reticular cell tumor	The name of this entity has been changed. "Tumor" is preferred over "sarcoma" because of the indolent nature of these lesions. Heterogeneity in lineage is recognized.

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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)

Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma*	Extranodal NK/T-cell lymphoma, **nasal type**

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

ICC

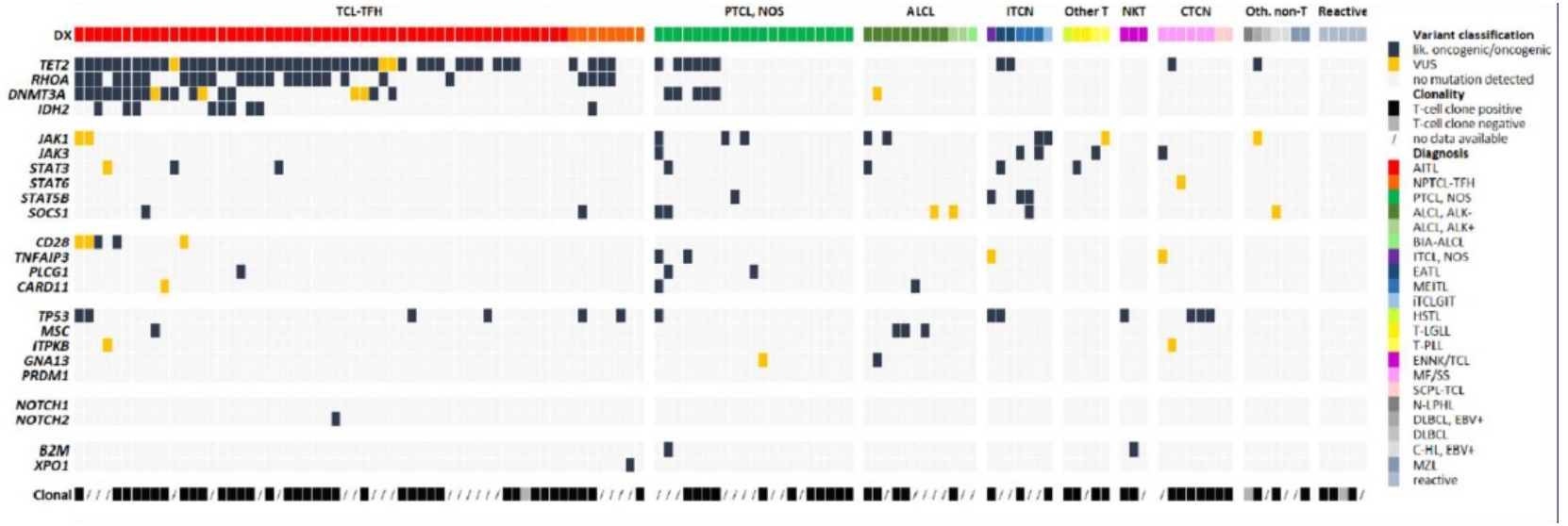
Type II refractory celiac disease*	Accepted as a precursor of enteropathy-associated T-cell lymphoma and has therefore been added to the classification.
Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract	Considered a definite entity. The name was changed to acknowledge its monoclonal nature. It may have neoplastic-type gene mutations and rearrangements and may progress to more aggressive disease.
Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract	Mutational studies provide evidence for the neoplastic origin. The term replaces both NK-cell enteropathy and lymphomatoid gastropathy.

WHO-HAEM 4th revised 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

ing *CD28*, *ICOS*, and *VAV1* have been reported.[256] Overall, the combinatory pattern of mutations in genes related to epigenetics and TCR signaling is a feature common to all nodal lymphomas of TFH origin. These lymphomas show a better response to histone deacetylase inhibitors compared with other PTCLs, which suggests the clinical relevance of the TFH phenotype.[257-259] For these reasons, the ICC unifies systemic lymphomas of TFH origin as a single entity—TFH lymphoma—with 3 subtypes: angioimmunoblastic-type (AITL), follicular-type, and NOS. By definition, this entity is restricted to patients with primary nodal or systemic disease and excludes primary cutaneous small or medium $CD4^+$ T-cell LPDs or other specified subtypes of cutaneous lymphomas with a TFH phenotype.[260] The criteria for distinguishing the 3 TFH lymphoma subtypes remain essentially unchanged and rely mainly on morphology and immunoarchitecture, especially the tumor microenvironment and distribution of FDCs. For establishing the TFH immunophenotype, which is critical for the diagnosis of TFH lymphomas of follicular type and NOS, we recommend the use of a 5-marker panel. Because $RHOA^{G17V}$ or $IDH2^{R172}$ are so characteristic of TFH lymphomas, especially of the AITL type, NGS studies are valuable in supporting a diagnosis of TFH lymphoma.[261]

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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“ NO CLASSIFICATION IS PERFECT NOT IT IS LIKELY THAT IT WILL EVER BE. ALL CLASSIFICATIONS DEPEND ON OUR KNOWLEDGE OF THE PATHOLOGY… SINCE THIS KNOWLEDGE IS FAR FROM PERFECT OR COMPLETE, NO CLASSIFICATION CAN BE OTHER THAN A REASONABLE WORKING COMPROMISE”

AZZOPARDI JG, Problems in breast pathology, 1979