The young side of LYMPHOMA

gli under 40 a confronto

Pescara, Auditorium Petruzzi
11-12 ottobre 2024

Linfoma di Hodgkin a Predominanza Linfocitaria: Nuova Classificazione WHO vs ICC 2022

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No Disclosures

NLPHL: Introduction

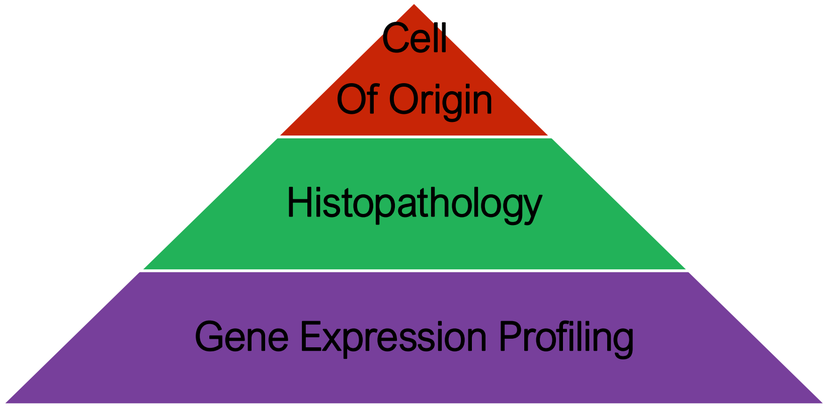
- Around 5% of all HLs
- M:F = 3:1
- Median age at presentation: 30-40 yrs
- Localized disease: 60-70% stage I-II
- Advanced stage: 30-40% stage III-IV (especially so called «variant patterns»)
- Transformation to B-NHL: ~5% (especially so called «variant patterns»)

NLPHL: General histopathologic aspects

- B cell neoplasm with paucity of large neoplastic cells: «lymphocyte predominant» (LP) cells or «pop corn» cells
- Abundance of background inflammatory cells
- Pattern of growth: predominantly nodular
- From first description (1947) included within HL: «*Hodgkin Paragranuloma*» ->> «*Nodular Lymphocyte Predominant HL*»

ICC 2022: NLPHL renamed «Nodular Lymphocyte Predominant B-cell Lymphoma»

WHO 2022: NLPHL retains its name «as not to interfere with ongoing trials». However, it may be more accurately called «Nodular Lymphocyte Predominant B-cell Lymphoma»



I. Cell of Origin

NLPHL and cHL Derive from Germinal Center B Cells

NLPHL

The NEW ENGLAND JOURNAL of MEDICINE

Origin of Nodular Lymphocyte-Predominant Hodgkin's Disease from a Clonal Expansion of Highly Mutated Germinal-Center B Cells

Authors: Theresa Marafioti, M.D., Michael Hummel, Ph.D., Ioannis Anagnostopoulos, M.D., Hans-Dieter Foss, M.D., Brunangelo Falini, M.D., Georges Delsol, M.D., Peter G. Isaacson, M.D., Stefano Pileri, M.D., and Harald Stein,

N Engl J Med. 1997 Aug 14;337(7):453-8.

PNAS

Hodgkin and Reed–Sternberg cells in lymphocyte predominant Hodgkin disease represent clonal populations of germinal center–derived tumor B cells

A Braeuninger [1], R Küppers, J G Strickler, H H Wacker, K Rajewsky, M L Hansmann

Proc Natl Acad Sci U S A. 1997 Aug 19;94(17):9337-42.

cHL

JEM Journal of Experimental Medicine

Hodgkin and Reed-Sternberg cells in Hodgkin's disease represent the outgrowth of a dominant tumor clone derived from (crippled) germinal center B cells.

H Kanzler, R Küppers, M L Hansmann, K Rajewsky

J Exp Med. 1996 Oct 1;184(4):1495-505.

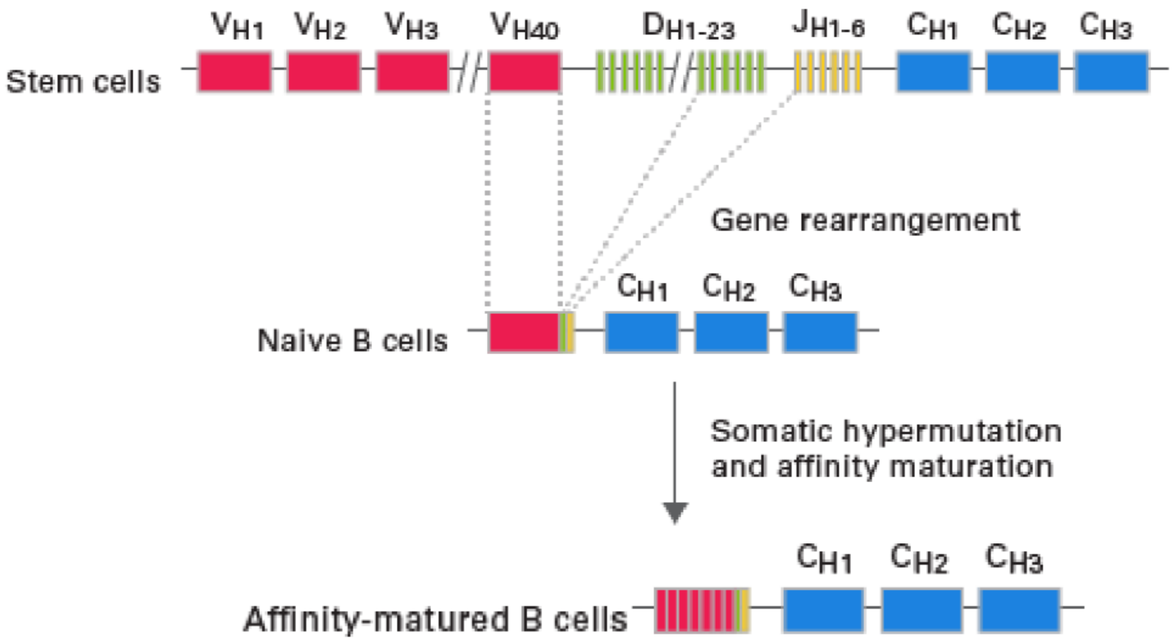
blood

Hodgkin and Reed-Sternberg cells represent an expansion of a single clone originating from a germinal center B-cell with functional immunoglobulin gene rearrangements but defective immunoglobulin transcription

Theresa Marafioti, Michael Hummel, Hans-Dieter Foss, Helmut Laumen, Petra Korbjuhn, Ioannis Anagnostopoulos, Hetty Lammert, Gudrun Demel, Jan Theil, Thomas Wirth, and Harald Stein

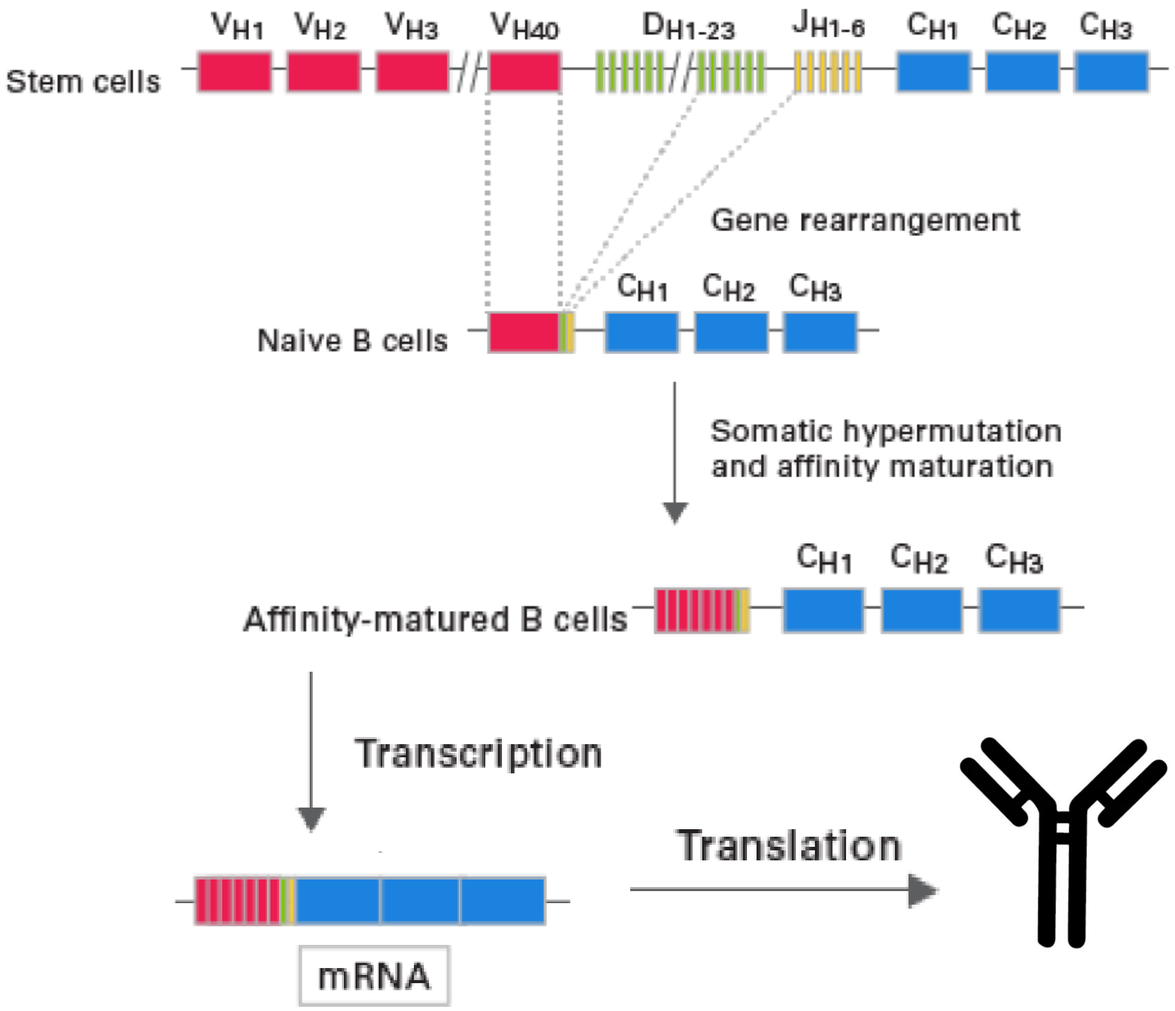
Blood. 2000 Feb 15;95(4):1443-50.

NLPHL and cHL Derive from Germinal Center B Cells



- PCR on DNA extracted from purified CD30+ cells (cHL) and CD20+ cells (NLPHL)
- Sequencing of V_H genes
- V_H gene amplification products derived from HRS/ LP cells identical in each patient
- Evidence of somatic hypermutations

NLPHL and cHL Have Different Ig Protein Expression



NLPHL

Ig gene transcription/ translation effective =

LPs show Ig expression at mRNA/ protein level

- Dependence from antigenic stimulation
- Intraclonal diversity in rearranged Ig genes

cHL

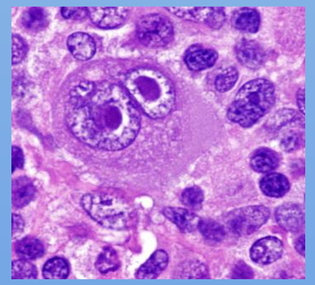
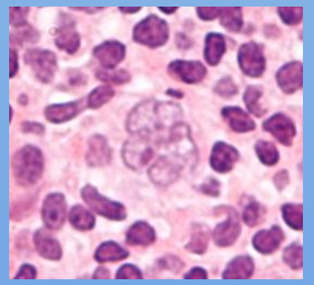
Ig gene transcription/ translation ineffective =

HRS lack Ig expression at mRNA/ protein level

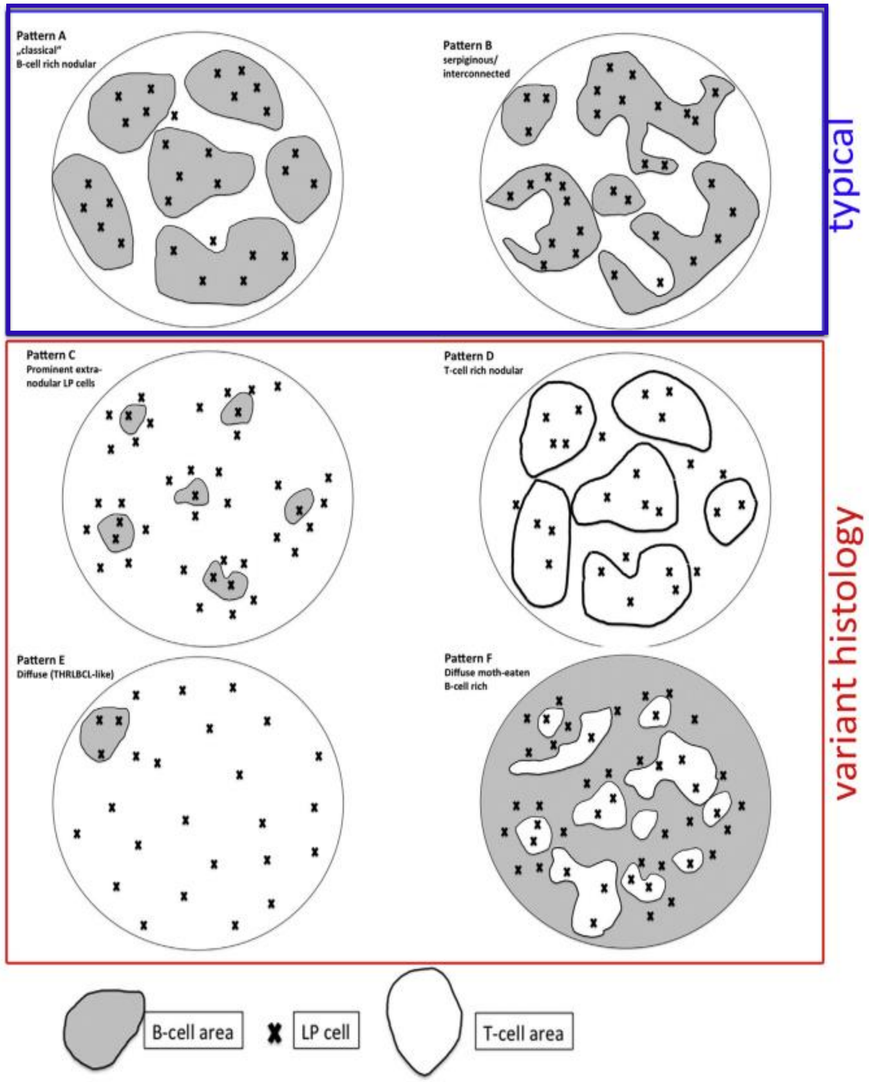
- Independence from antigenic stimulation
- Upregulation of anti-apoptotic pathways
- No intraclonal diversity

II. Histopathologic aspects

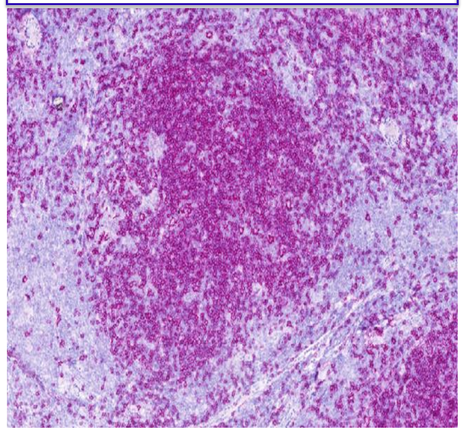
NLPHL and cHL have distinct morphology and immunophenotype

	cHL	NLPHL
Neoplastic cell	 Hodgkin/ Reed Sternberg (HRS)	 Lymphocyte-Predominant (LP)
Phenotype	CD20-, CD79a-, PAX5+	CD20+, CD79a+, PAX5+
	CD30+, CD15+	CD30-, CD15-
	Oct2-, BOB1-	Oct2+, BOB1+
	PD-L1+	PD-L1-
EBV status	~20% EBV+ (Mixed Cellularity)	EBV negative
Background	More heterogeneous	Lymphs/Histiocytes

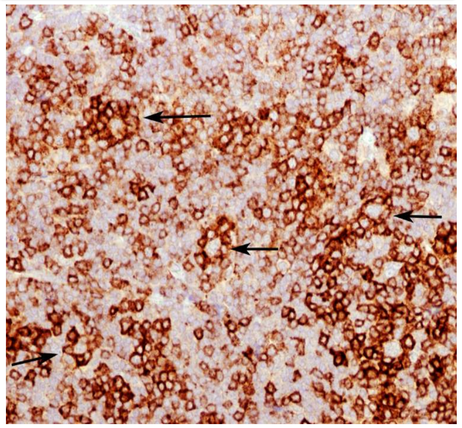
Variant histologic patterns in NLPHL



Pattern A, CD20



Pattern A, PD1

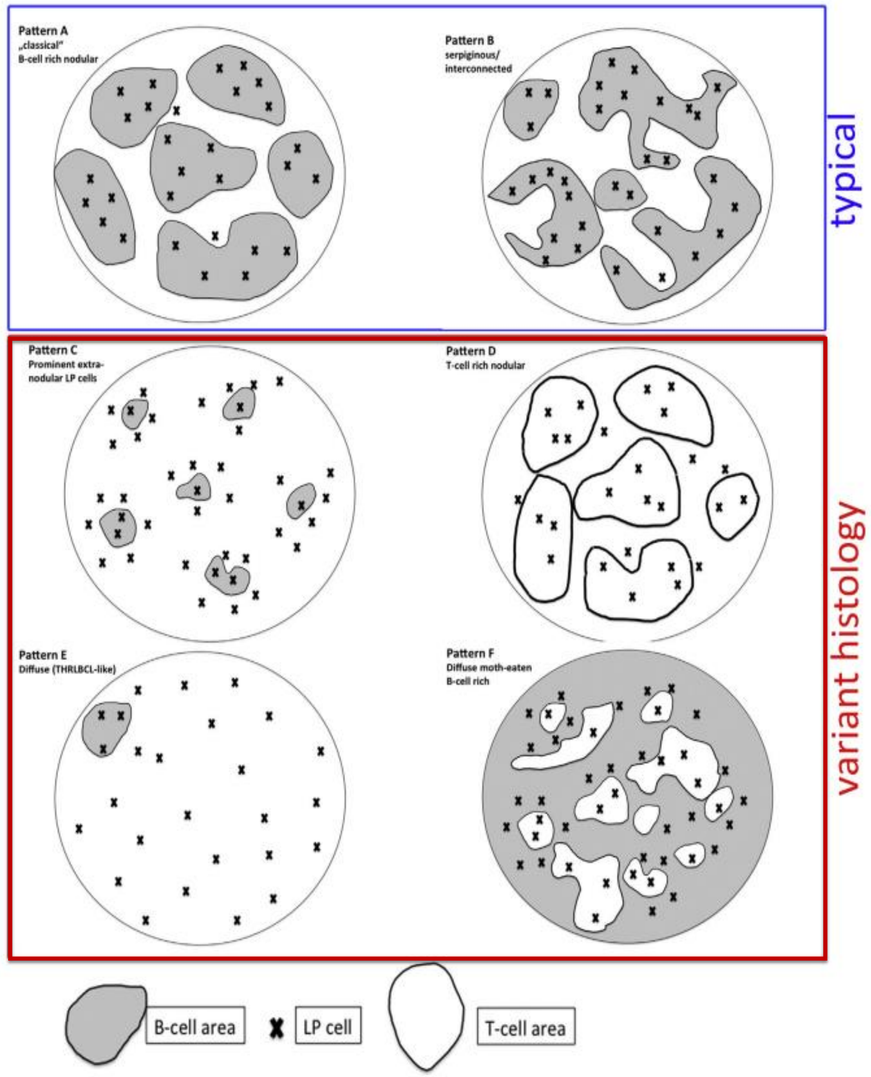


Typical A/B Patterns

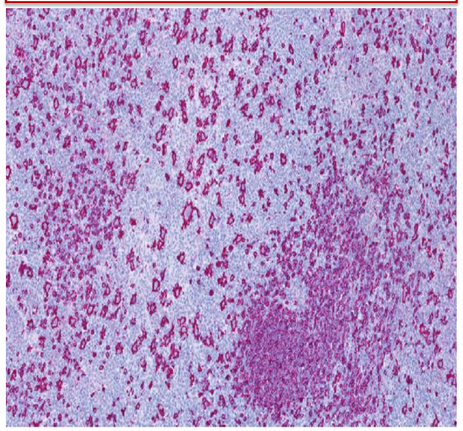
- Most common patterns in NLPHL
- Nodular architecture with FDC meshworks
- LP cells embedded in a B cell rich environment
- Fewer CD4/PD1 ^{pos} T rosetting around LP cells

- More common limited stage
- Rarer progression into aggressive B-NHL

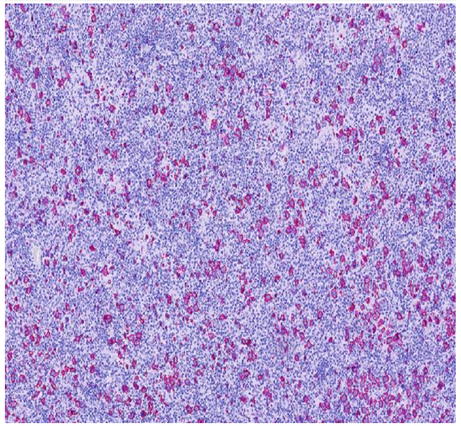
Variant histologic patterns in NLPHL



Pattern C, CD20



Pattern E, CD20

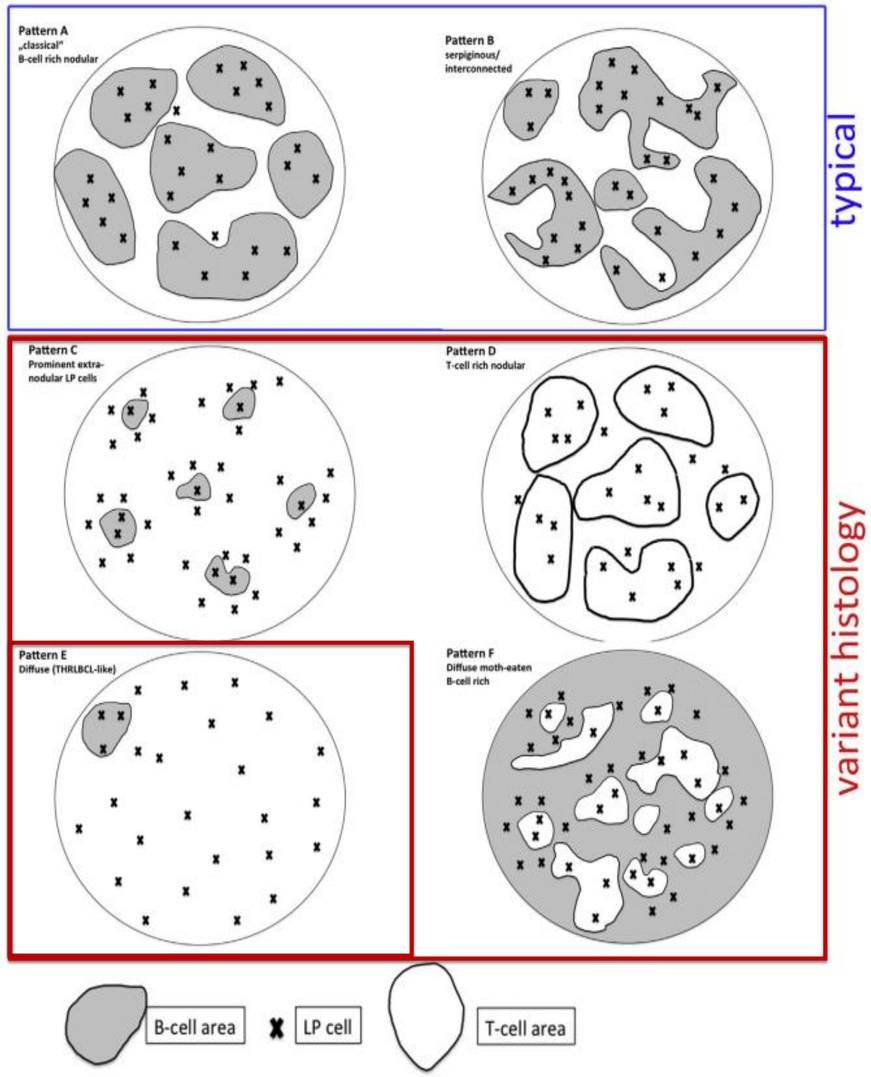


Variant C-F Patterns

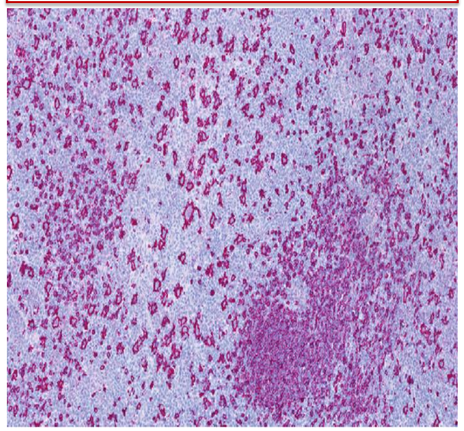
- Rarer patterns in NLPHL
- Variable reduction/ loss of nodular architecture
- Progressive reduction of B lymphocytes
- LP cells embedded in a T cell rich environment

- More common advanced stage
- Higher propensity to progress in B-NHL

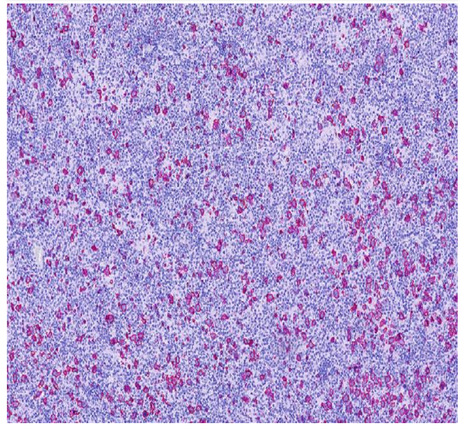
Variant histologic patterns in NLPHL



Pattern C, CD20



Pattern E, CD20



Variant E Pattern

- Also known as «THRLBL-like NLPHL»
- Similar cell composition to THRLBL *de novo*
- «Distinction from THRLBL relies on at least one unequivocal nodule with features of NLPHL»

blood®
Volume 122, Issue 26, 19 December 2013, Pages 4246-4252

CME Article

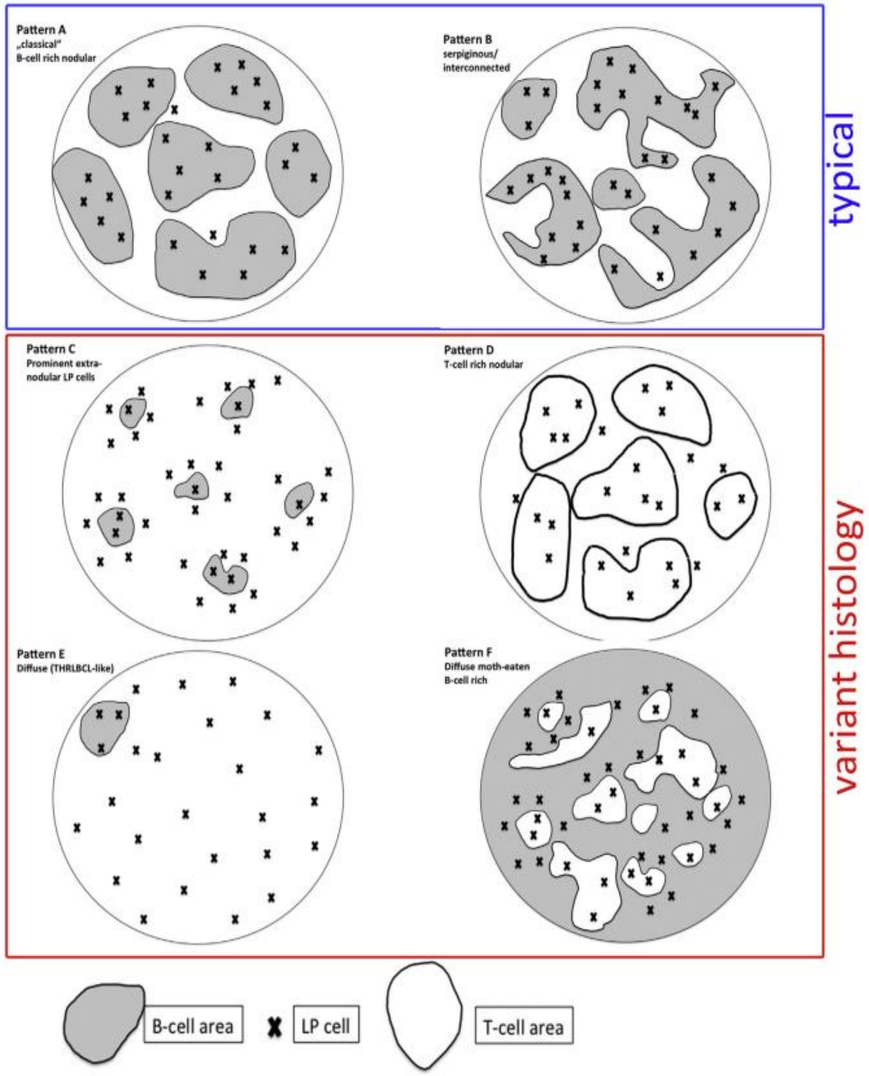
The prognostic impact of variant histology in nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group (GHSG)

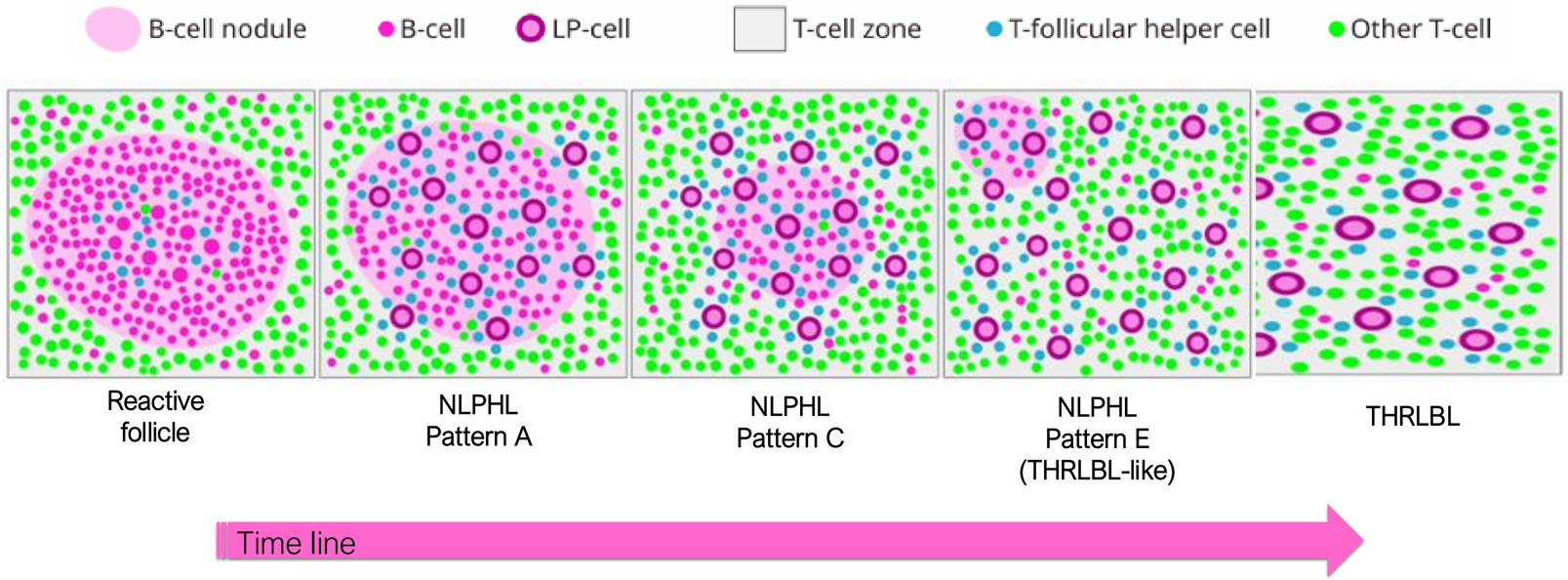
Sylvia Hartmann [1], Dennis A. Eichenauer [2, 3], Annette Plütschow [2, 3], Anja Mottok [4], Roshanak Bob [5], Karoline Koch [6], Heinz-Wolfram Bernd [7], Sergio Cogliatti [8], Michael Hummel [9], Alfred C. Feller [7], German Ott [10], Peter Möller [11], Andreas Rosenwald [4], Harald Stein [5], Martin-Leo Hansmann [1], Andreas Engert [2, 3], Wolfram Klapper [6]

Table 2. Clinical parameters of typical NLPHL patients compared with histopathologic NLPHL variants

	Typical NLPHL (pattern A/B), n = 308%	NLPHL variant pattern (non-A/B), n = 105%	Fisher exact test
Clinical stages III/IV or IIB with a large mediastinal mass and/or extranodal disease	14.6	29.5	$P = .0012$
International Prognostic Score (IPS) ≥3*	3.3	14.3	$P = .0005$
Male gender	72.4	79.0	n.s.
Stage IV	1.9	11.4	$P = .0002$
Age ≥45 y	38.6	29.5	n.s.
Albumin <4 g/dL	10.7	18.8	n.s.
Hemoglobin <10.5 g/dL	0.7	4.8	$P = .0136$
Leukocytes >15 000/mm^3	0.3	1.0	n.s.
Lymphocytes <600/mm^3	0.7	1.0	n.s.
Splenic involvement	6.7	3.2	n.s.
Disease progression or relapse in the first 5 years after study enrollment in the GHSG	6.5	18.1	$P = .0009$

Pattern of Transformation/ Evolution in NLPHL





- Patterns of NLPHL are not static, but can evolve over time
- Transformation/evolution is associated with a switch from a «B-cell rich» to a «T cell/histiocyte rich» microenvironment
- NPLHL- Pattern E can be regarded as a «precursor» of some THRLBL

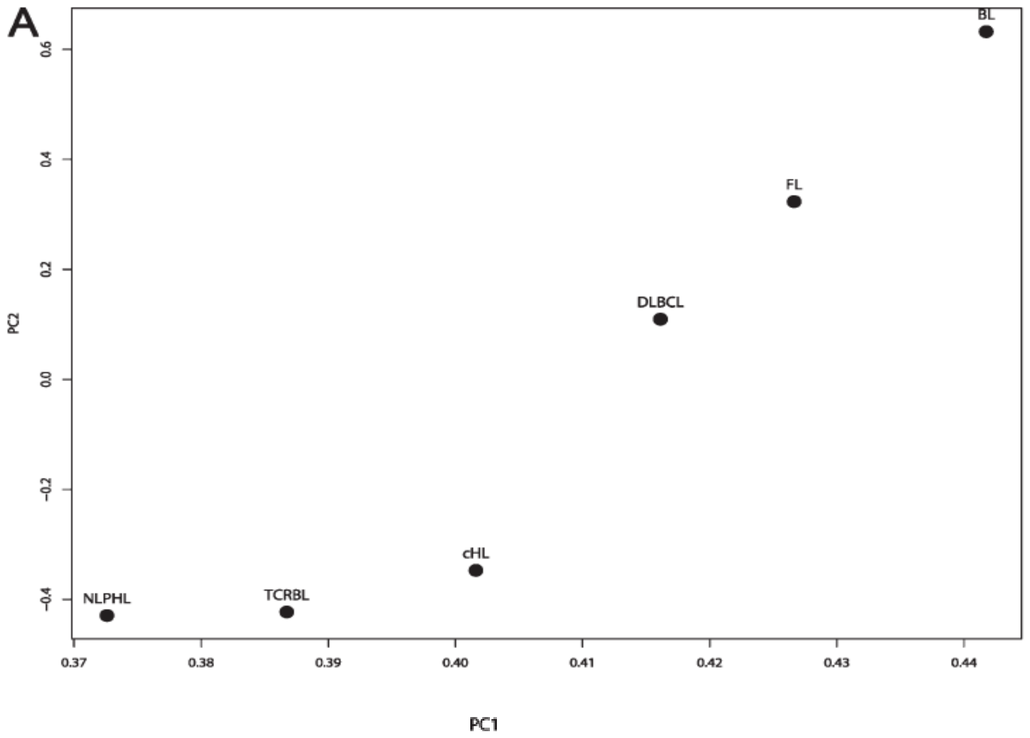
III. Gene Expression Profiling

Origin and pathogenesis of nodular lymphocyte–predominant Hodgkin lymphoma as revealed by global gene expression analysis

J Exp Med (2008) 205 (10): 2251–2268.

Verena Brune, Enrico Tiacci, Ines Pfeil, Claudia Döring, Susan Eckerle, Carel J.M. van Noesel, Wolfram Klapper, Brunangelo Falini, Anja von Heydebreck, Dirk Metzler, Andreas Bräuninger, Martin-Leo Hansmann, Ralf Küppers

GEP of tumor cells in Germinal Center Derived B-NHL

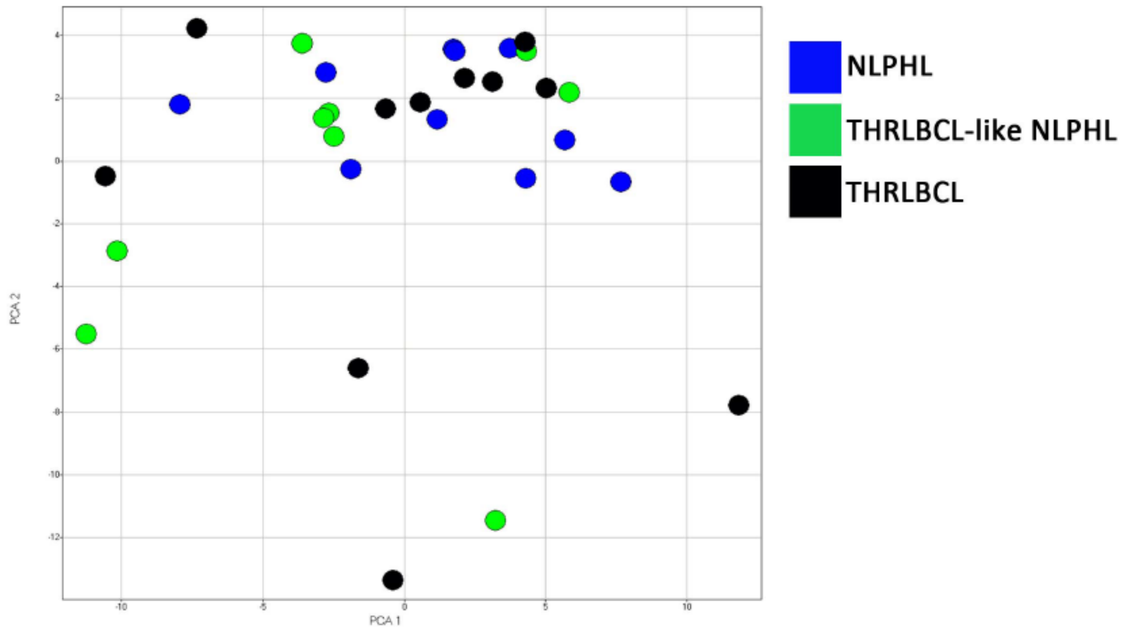


Nodular Lymphocyte Predominant Hodgkin Lymphoma and T Cell/Histiocyte Rich Large B Cell Lymphoma - Endpoints of a Spectrum of One Disease?

PLoS One. 2013 Nov 11;8(11):e78812.

Sylvia Hartmann[1]*, Claudia Döring[1], Christina Jakobus[1], Benjamin Rengstl[1], Sebastian Newrzela[1], Thomas Tousseyn[2], Xavier Sagaert[2], Maurilio Ponzoni[3], Fabio Facchetti[4], Chris de Wolf-Peeters[2], Christian Steidl[5], Randy Gascoyne[5], Ralf Küppers[6], Martin-Leo Hansmann[1]

GEP of tumor cells in NLPHL, THRLBCL-like NLPHL and THRLBCL



Nodular Lymphocyte Predominant Hodgkin Lymphoma and T Cell/Histiocyte Rich Large B Cell Lymphoma - Endpoints of a Spectrum of One Disease?

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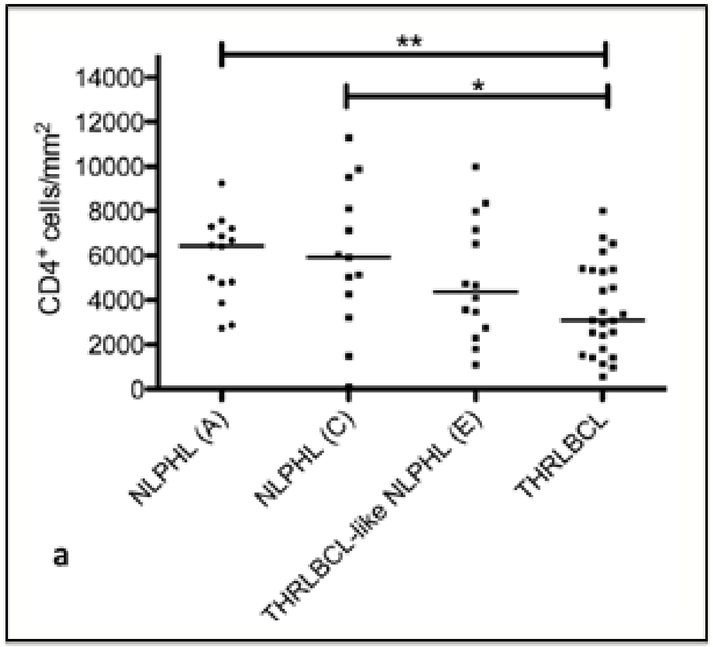
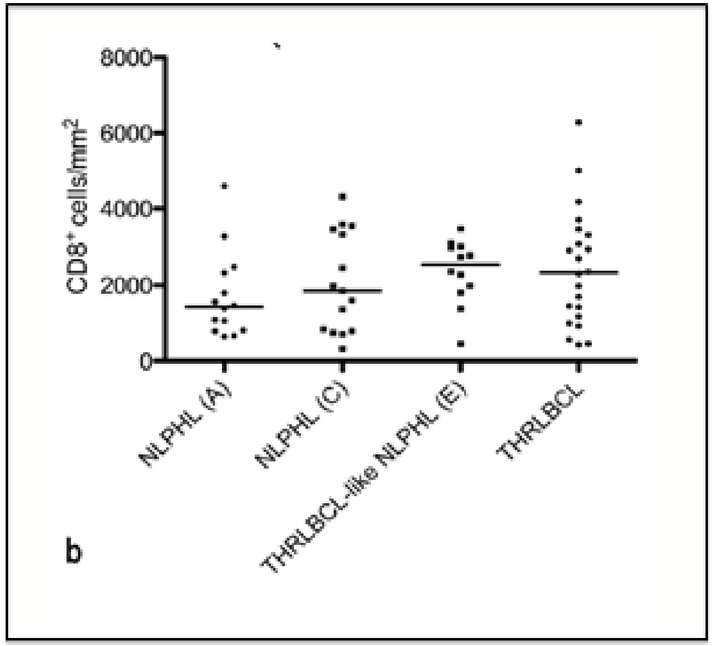
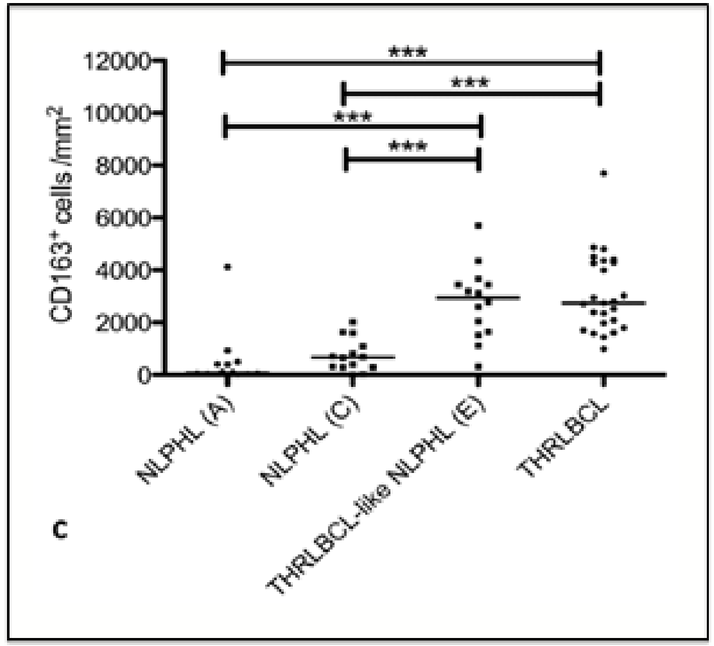
Quantification of the microenvironment in typical NLPHL (patterns A and C), THRLBCL-like NLPHL (pattern E) and THRLBCL







NLPHL- Conclusions

I. CELL OF ORIGIN:

- Germinal Center Derived B Cell Neoplasm with a retained dependence from antigen stimulation

II. HISTOPATHOLOGY:

- Distinct entity with defined histopathologic features compared to cHL and other B-NHL
- Identification of histopathologic patterns has relevant prognostic implications
- «Dinamic entity» with progression associated mostly with a modification in tumor microenvironment

III. GENE EXPRESSION PROFILING:

- GEP of LP cells similar to HRS and other B-NHL, especially THRLBL

Classification of NLPHL… a matter of point of view

The Conservatives

The Progressives

The Italians' Approach

References

Brune V, Tiacci E, Pfeil I, et al. Origin and pathogenesis of nodular lymphocyte-predominant Hodgkin lymphoma as revealed by global gene expression analysis. J Exp Med. 2008;205(10):2251-2268.

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Stein H, Marafioti T, Foss HD, et al. Down-regulation of BOB.1/OBF.1 and Oct2 in classical Hodgkin disease but not in lymphocyte predominant Hodgkin disease correlates with immunoglobulin transcription. *Blood*. 2001;97(2):496-501

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Panayi C, Akarca AU, Ramsay AD, et al. Microenvironmental immune cell alterations across the spectrum of nodular lymphocyte predominant Hodgkin lymphoma and T-cell/histiocyte-rich large B-cell lymphoma. *Front Oncol*. 2023;13:1267604.

… Grazie