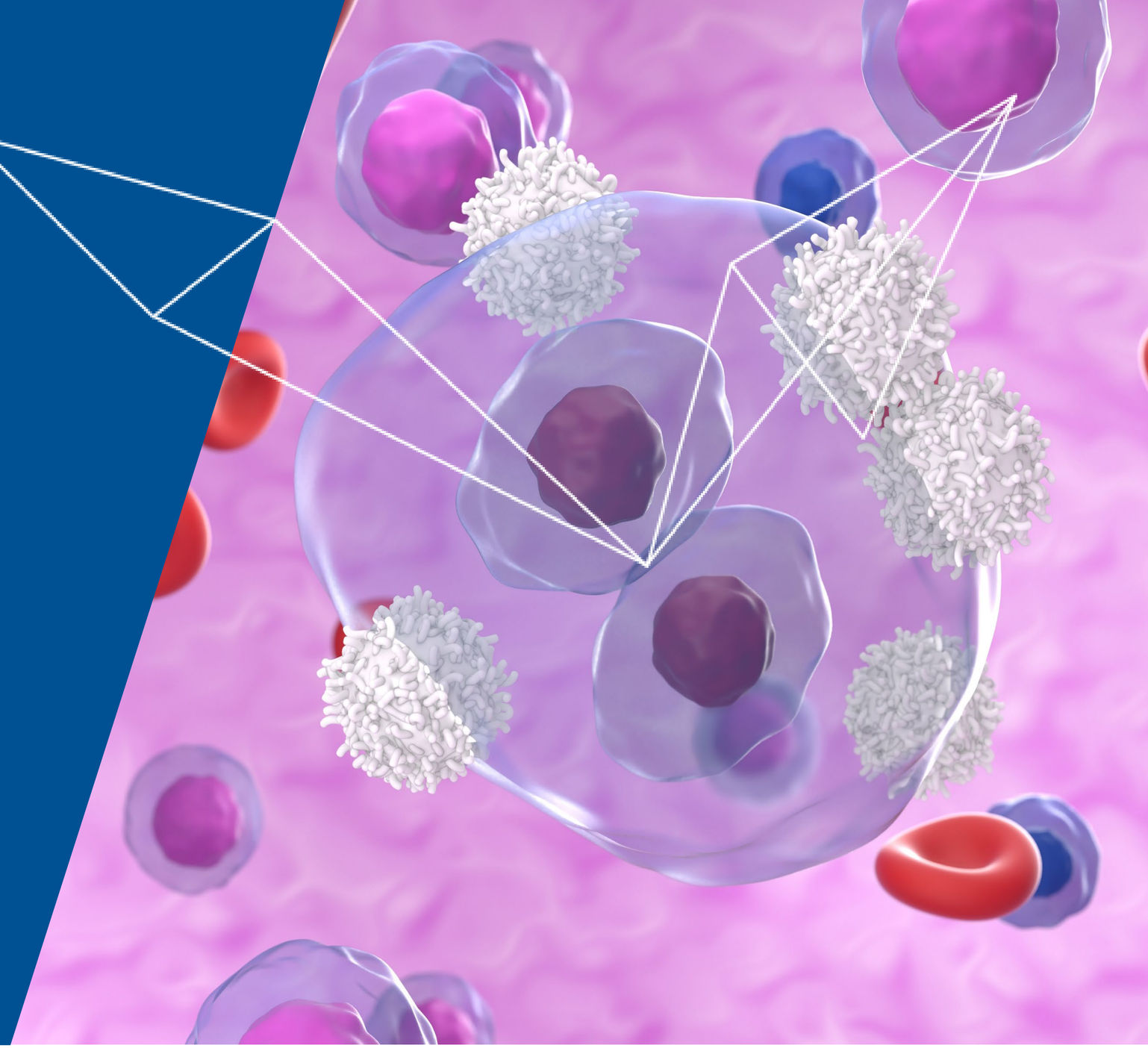
EHA EUROPEAN HEMATOLOGY ASSOCIATION

Hodgkin Lymphoma histology

Miguel Angel Piris

EHA-MSH Tutorial

April, 2024

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Disclosures

- Millenium/Takeda: Advisory Board, Lecture Fees, Research Funding
- Celgene: Advisory Board
- Gilead: Advisory Board; Research funding
- Jansen: Advisory Board; Lecture Fees
- Nanostring: Advisory Board
- Kyowa Kirin: Advisory Board
- Kura: Research Funding

Hodgkin lymphoma (HL) diagnosis

Objectives:

1.- Criteria for the diagnosis of classical HL
2.- Other diseases where Sternberg-Reed cells can be found
3.- Therapeutic implications
4.- Terminology update

Miguel A Piris
Fundación Jiménez Díaz, Madrid, Spain

Thomas Hodgkin circa 1835

born 1798 Pentonville London

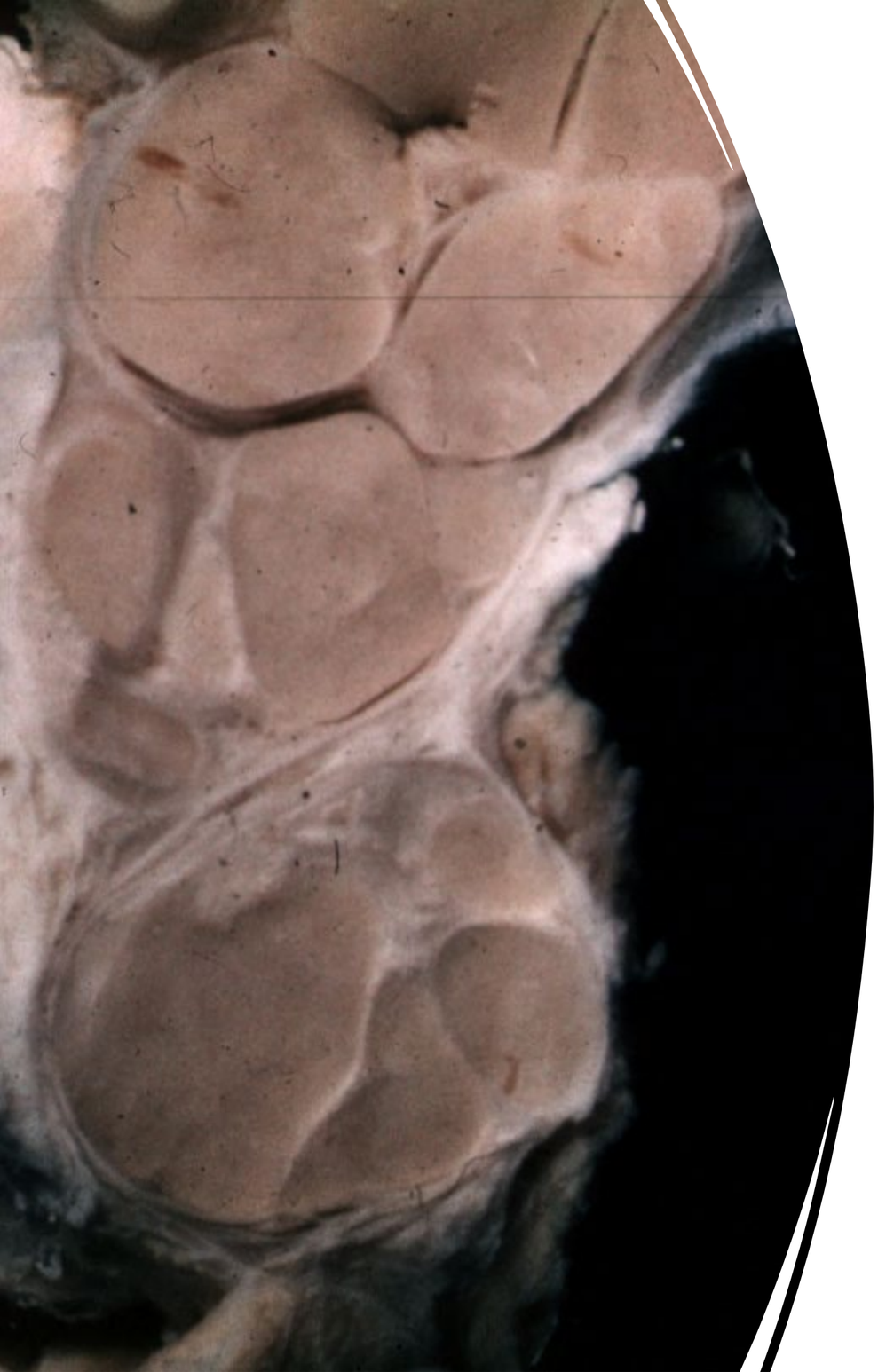
Quaker family

1819 Guy’s

1820 Edinburgh

1825 lecturer in morbid anatomy and curator of the museum Guy’s

Fellow members of staff: Richard Bright, Thomas Addison



The Disease:

paper first read before the
Medico-Chirugical Society of London
January 10th 1832

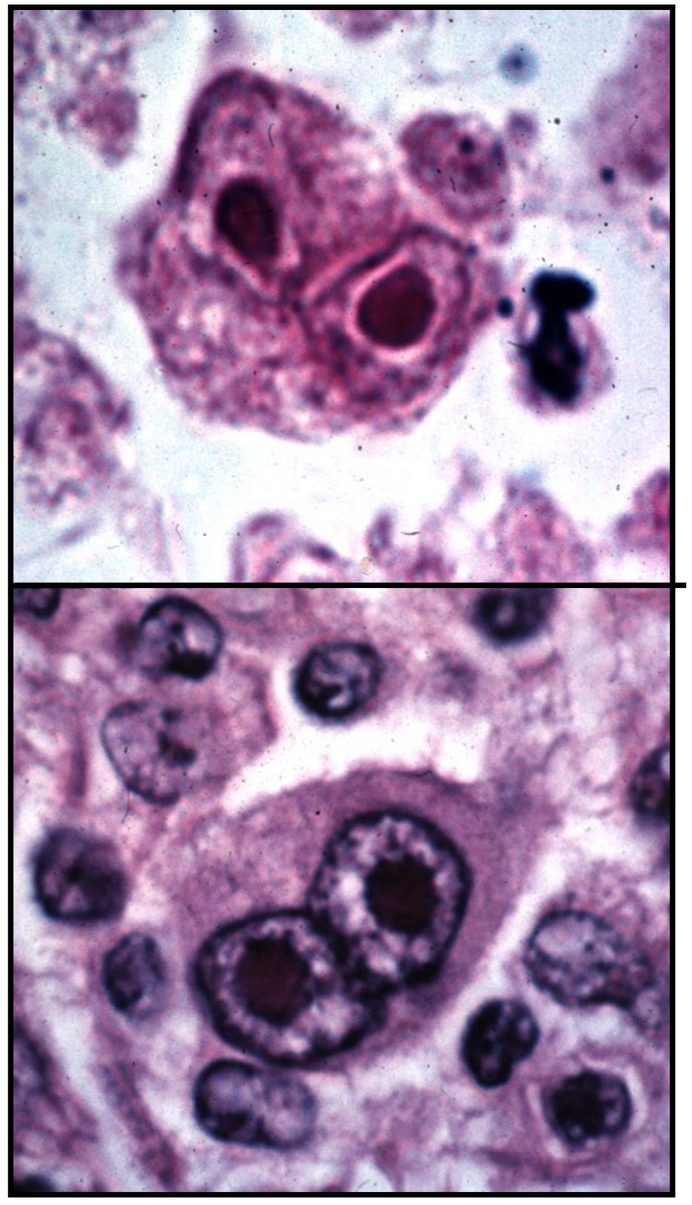
6 cases from Guy's Museum and 1 from UCH

"enlargement of the glands appeared to be a primitive affection of those bodies, rather than the result of an irritation... from some ulcerated surface or other inflamed texture."

The Disease:

- 1926 Fox examined 3 cases microscopically
- 2 were Hodgkin's Disease
- 1 was considered as non-Hodgkin's lymphoma

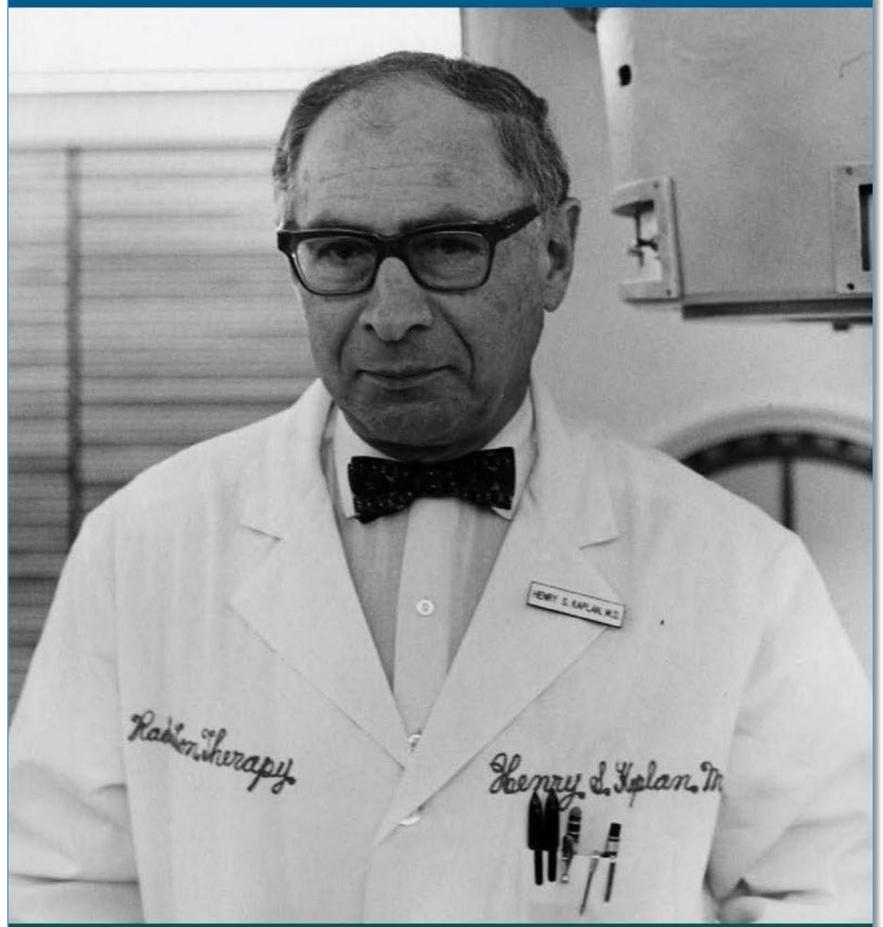
1832



modern

Henry Kaplan

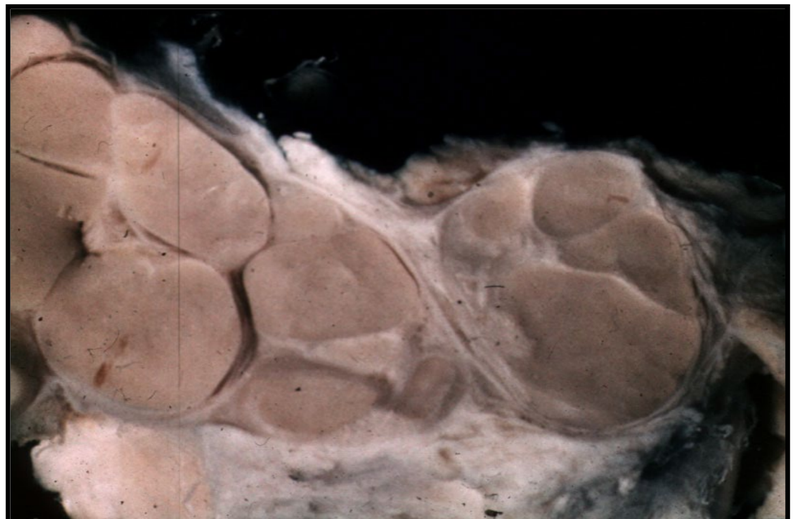
and the Story of Hodgkin's Disease

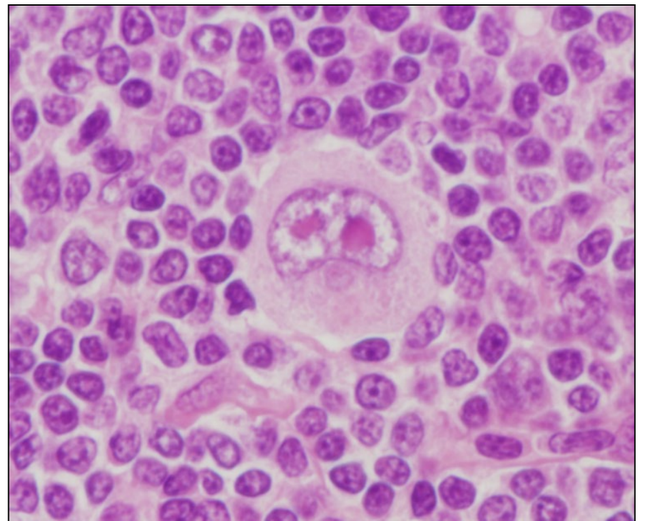


Charlotte DeCroes Jacobs

WHO/ICC Classification of Hodgkin Lymphoma

- Nodular lymphocyte predominant B-cell lymphoma: CD20+, OCT2+, EBV-, CD30-, PD1 rosettes
- Classical Hodgkin lymphoma: CD30+
  - Nodular sclerosis CHL
  - Lymphocyte-rich CHL: PD1 rosettes
  - Mixed cellularity CHL
  - Lymphocyte depleted CHL





Hodgkin lymphoma

Hodgkin lymphoma, classical:

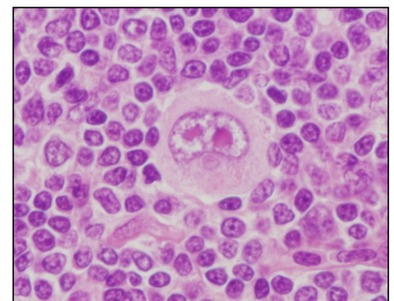
Nodal disorder, primarily in the Waldeyer region, cervical lymph nodes and mediastinum

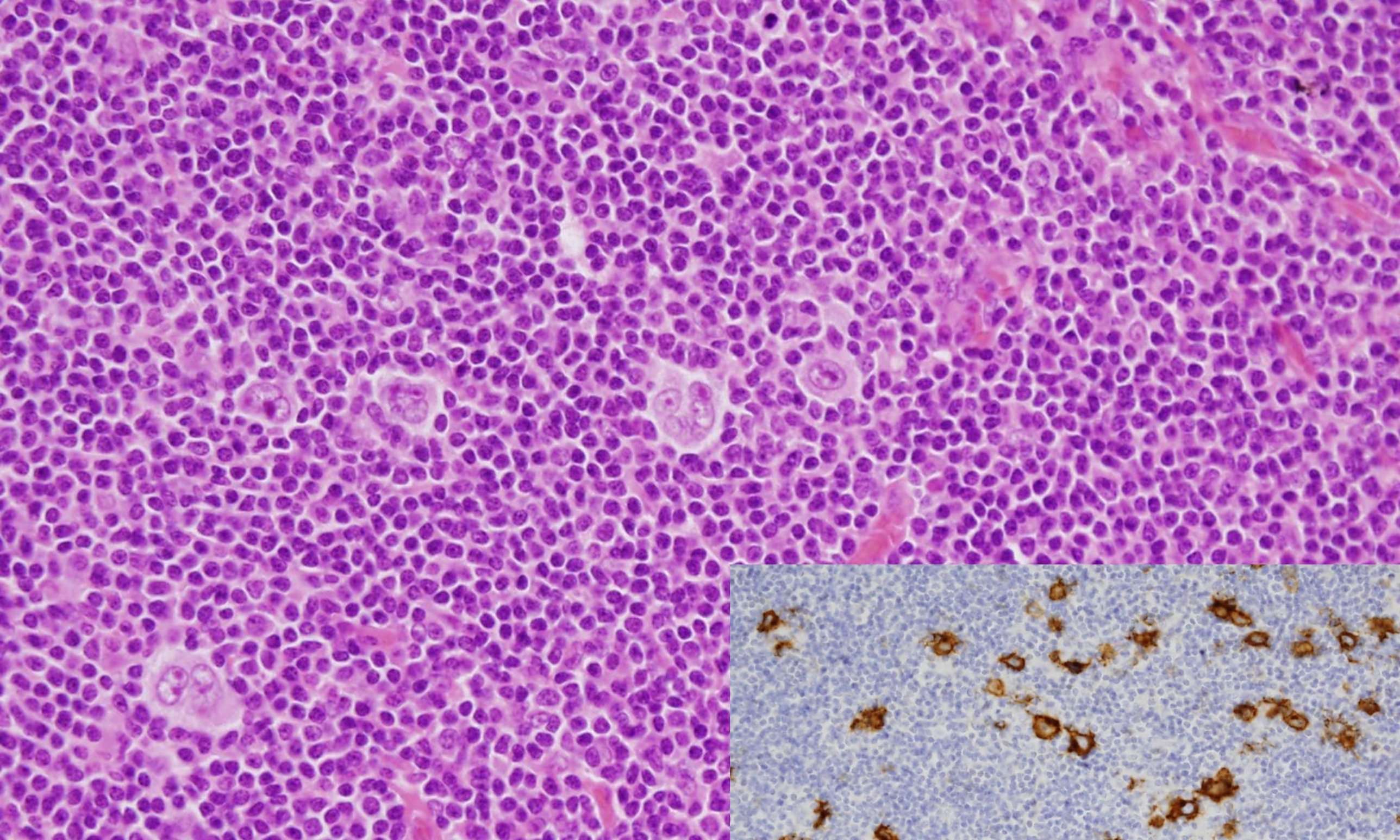
Hodgkin and Reed-Sternberg cells (or HRS cells) residing in an abundant heterogeneous admixture of inflammatory and accessory cells

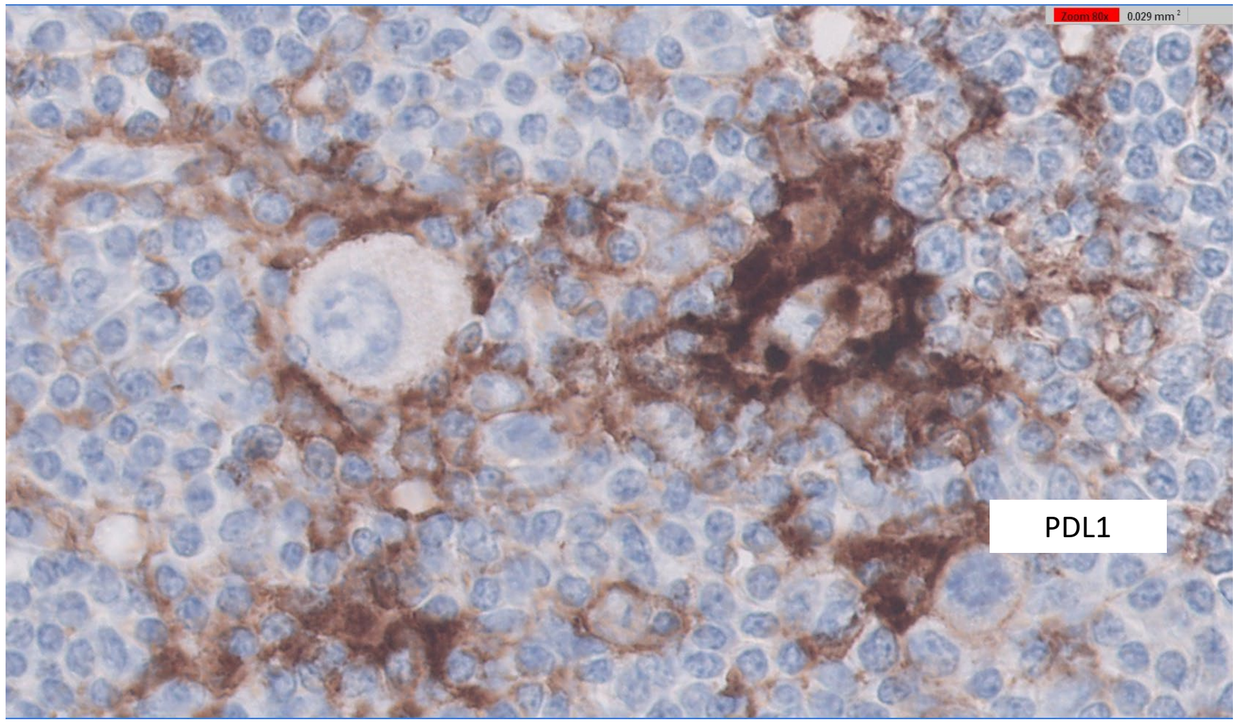
CD30+, PAX5+, CD15+ (2/3), EBV/LMP (1/3)

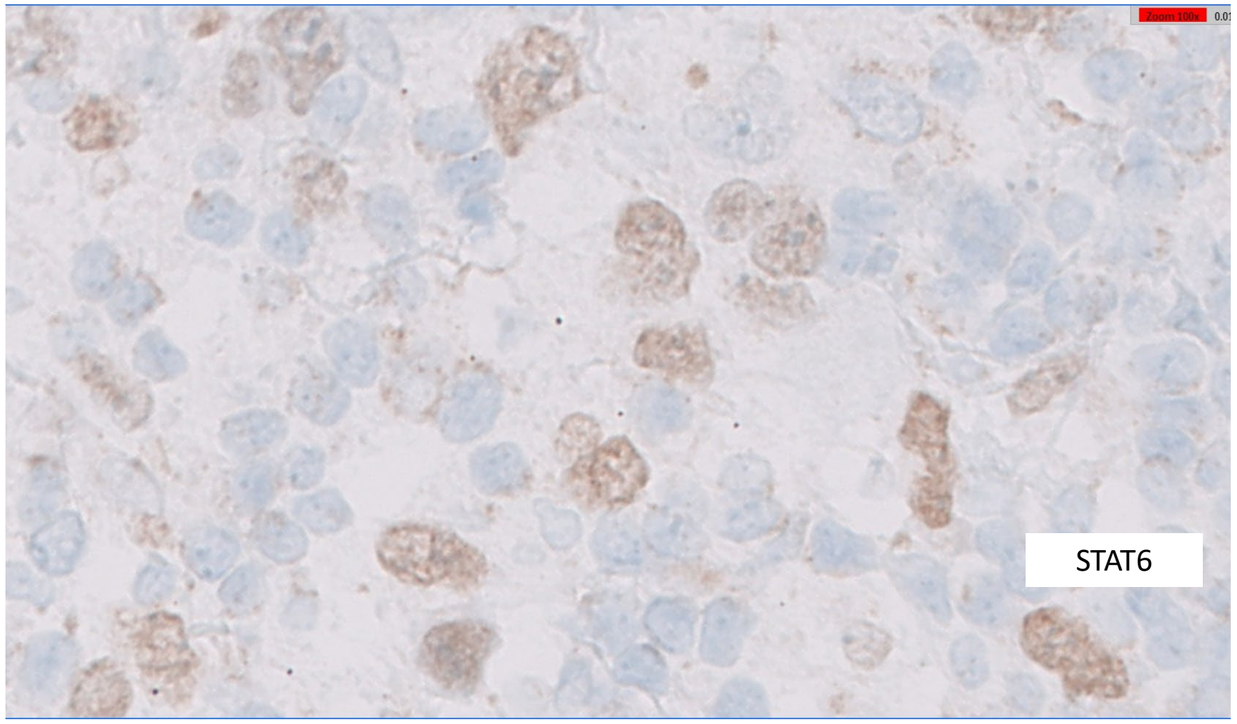
9p24 gains; STAT6/SOCS1 mt; B2M/HLA-I/CIITA,…

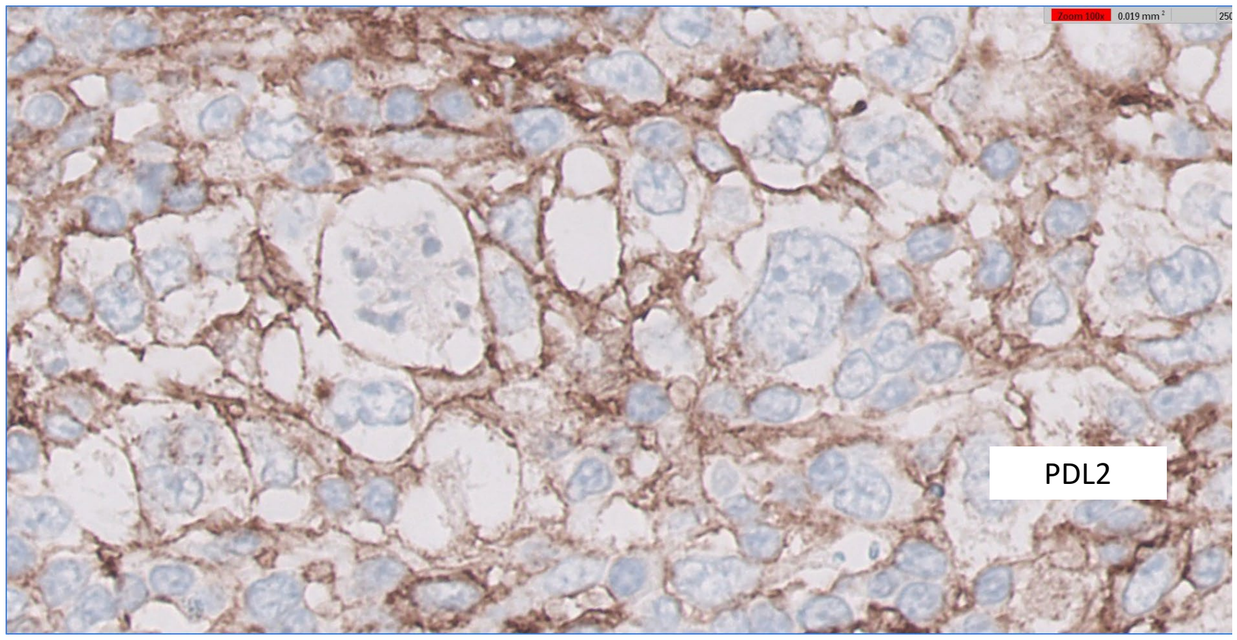
Tumour cells are often ringed by T lymphocytes in a rosette-like manner






Zoom 80x
0.029 mm²
PDL1


Zoom 100x
STAT6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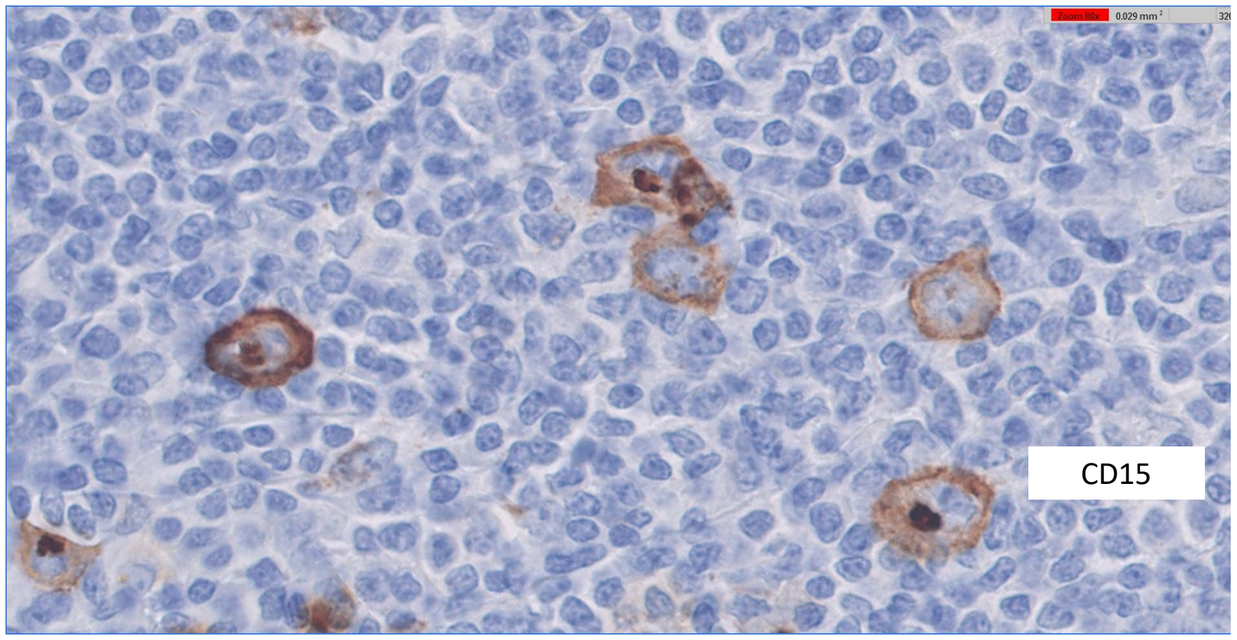
PDL2


Zoom 80x
0.029 mm²
CD15

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Nivolumab and brentuximab vedotin with or without bendamustine for R/R Hodgkin lymphoma in children, adolescents, and young adults

Paul Harker-Murray,[1,*] Christine Mauz-Körholz,[2,*] Thierry Leblanc,[3] Maurizio Mascarin,[4] Gérard Michel,[5] Stacy Cooper,[6] Auke Beishuizen,[7] Kasey J. Leger,[8] Loredana Amoroso,[9] Salvatore Buffardi,[10] Charlotte Rigaud,[11] Bradford S. Hoppe,[12] Julie Lisano,[13] Stephen Francis,[14] Mariana Sacchi,[14] Peter D. Cole,[15] Richard A. Drachtman,[15] Kara M. Kelly,[16,†] and Stephen Daw[17,†]

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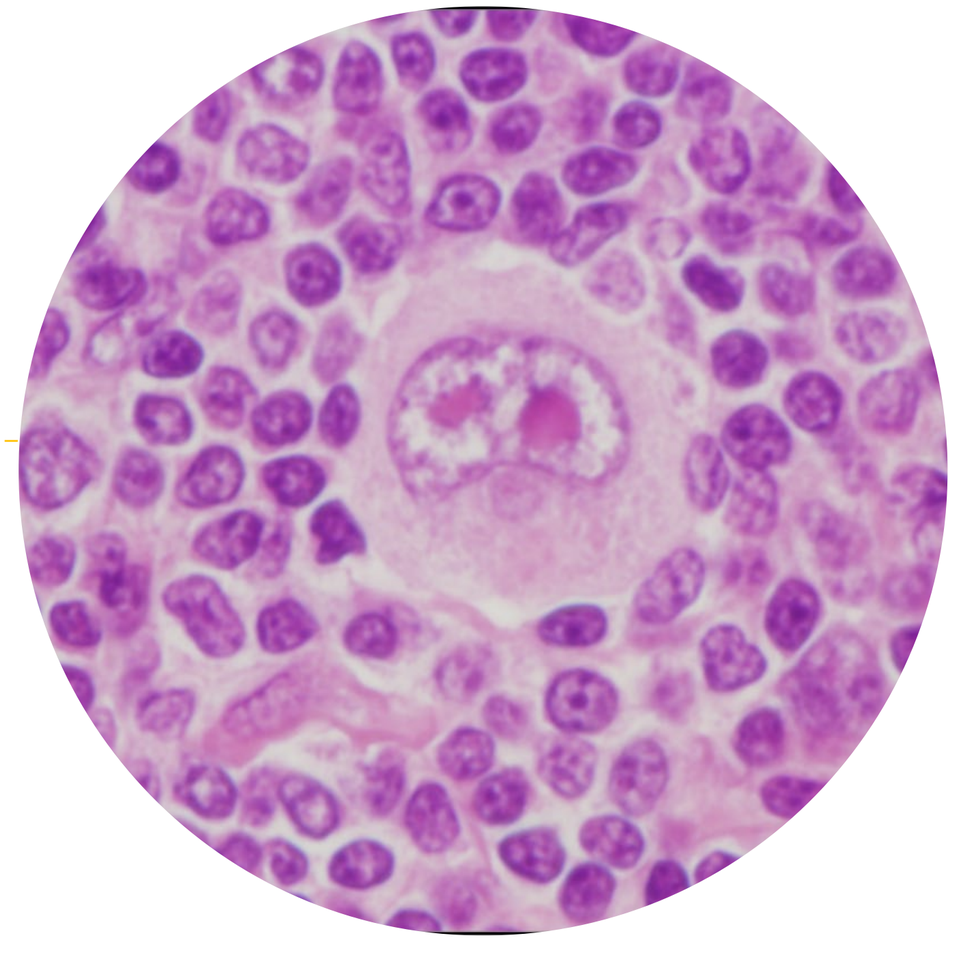
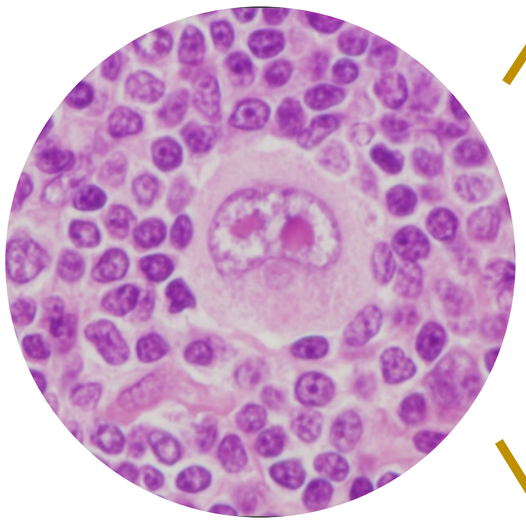
KEY POINTS

- A risk-stratified, response-adapted salvage strategy resulted in high CMR rates with limited toxicities in CAYA with R/R cHL.
- CMR rate after nivo + BV induction was 59% and increased to 94% with BV + bendamustine intensification.

Children, adolescents, and young adults (CAYA) with relapsed/refractory (R/R) classic Hodgkin lymphoma (cHL) without complete metabolic response (CMR) before autologous hematopoietic cell transplantation (auto-HCT) have poor survival outcomes. CheckMate 744, a phase 2 study for CAYA (aged 5-30 years) with R/R cHL, evaluated a risk-stratified, response-adapted approach with nivolumab plus brentuximab vedotin (BV) followed by BV plus bendamustine for patients with suboptimal response. Risk stratification was primarily based on time to relapse, prior treatment, and presence of B symptoms. We present the primary analysis of the standard-risk cohort. Data from the low-risk cohort are reported separately. Patients received 4 induction cycles with nivolumab plus BV; those without CMR (Deauville score >3, Lugano 2014) received BV plus bendamustine intensification. Patients with CMR after induction or intensification proceeded to consolidation (high-dose chemotherapy/auto-HCT per protocol). Primary end point was CMR any time before consolidation. Forty-four patients were treated. Median age was 16 years. At a minimum follow-up of 15.6 months, 43 patients received 4 induction cycles (1 discontinued), 11 of whom received intensification; 32 proceeded to consolidation. CMR rate was 59% after induction with nivolumab plus BV and 94% any time before consolidation (nivolumab plus BV ± BV plus bendamustine). One-year progression-free survival rate was 91%. During induction, 18% of patients experienced grade 3/4 treatment-related adverse events. This risk-stratified, response-adapted salvage strategy had high CMR rates with limited toxicities in CAYA with R/R cHL. Most patients did not require additional chemotherapy (bendamustine intensification). Additional follow-up is needed to confirm durability of disease control. This trial was registered at www.clinicaltrials.gov as #NCT02927769.

Sternberg-Reed or Hodgkin cells?





NSCHL

CD30
9p24,…
STAT6 mt,…
Mediastinal Grey Zone

Lymphocyte predominance
NLPBL

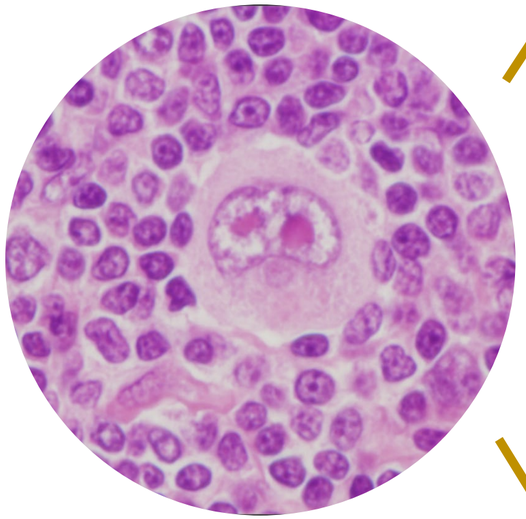
GC BCL
OCT2/TFH rosettes
CD20
THRBCL progression

HRS Cells in
PTCL

RHOA/IDH2 mt
TFH phenotype

HRS cells in
BCL (EBV)

PTLD
EBV+ LBCL



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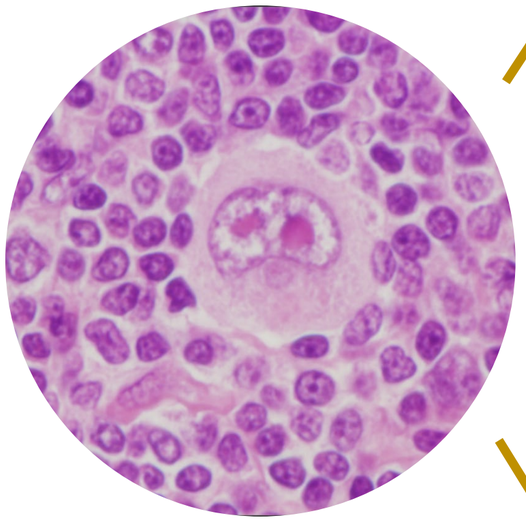

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THRBCL progression

HRS Cells in PTCL

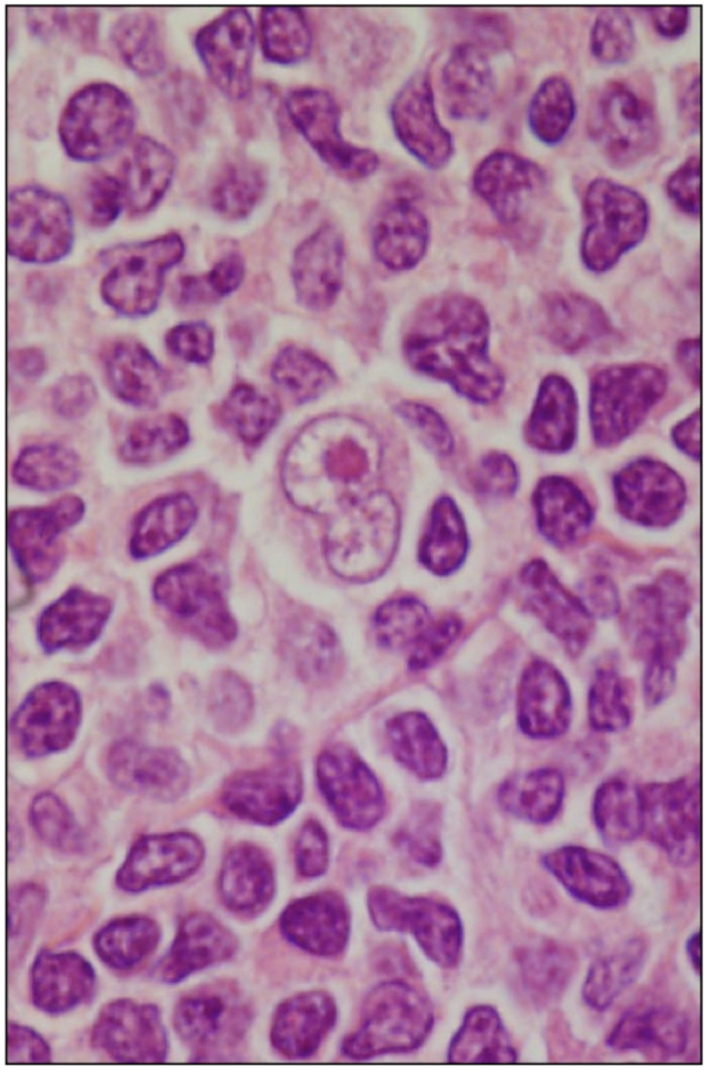
RHOA/IDH2 mt
TFH phenotype

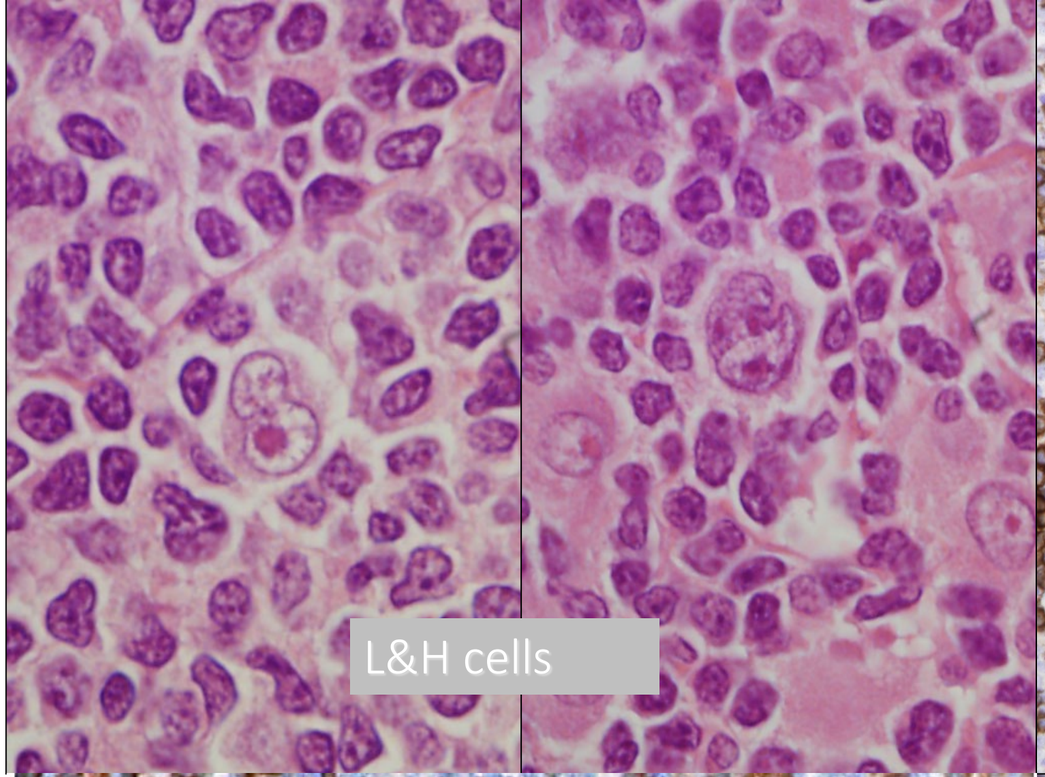
HRS cells in BCL (EBV)

PTLD
EBV+ LBCL

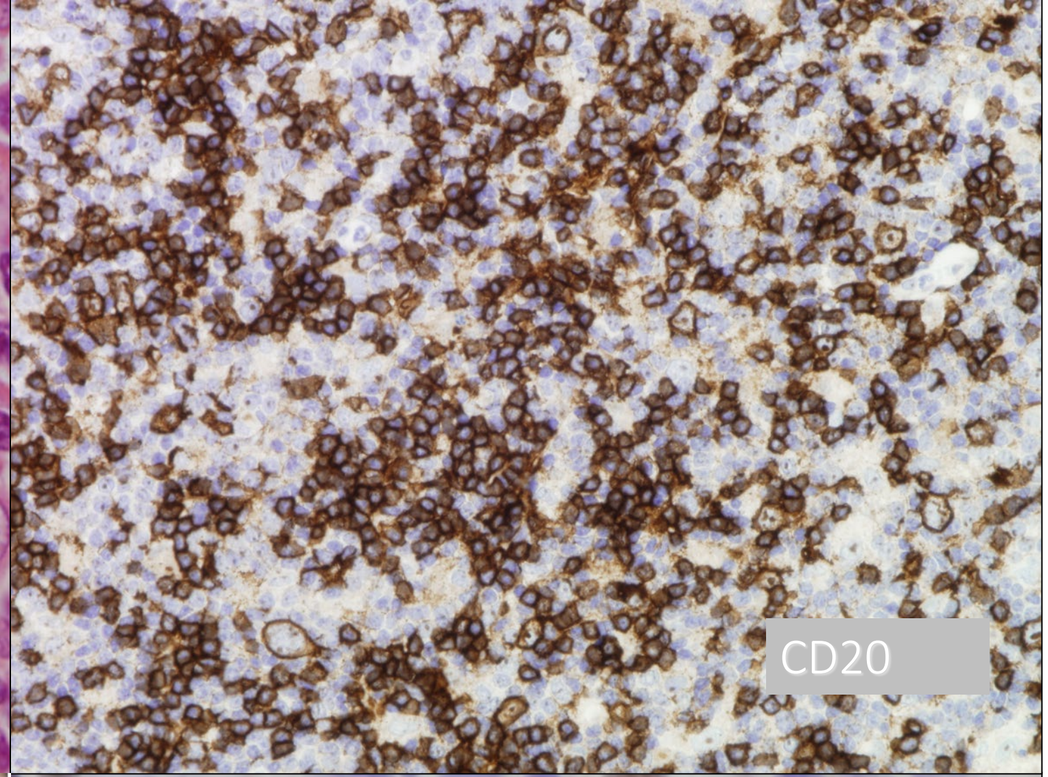
Nodular Lymphocyte Predominance B-cell Lymphoma

- CD20+ OCT2+ L&H cells
- Surrounded by PD1+ TFH rosettes
- Most cases diagnosed in stage I and II, with indolent course
- When diagnosed in advanced stages, is frequently an aggressive disorder, with THRBCL histology

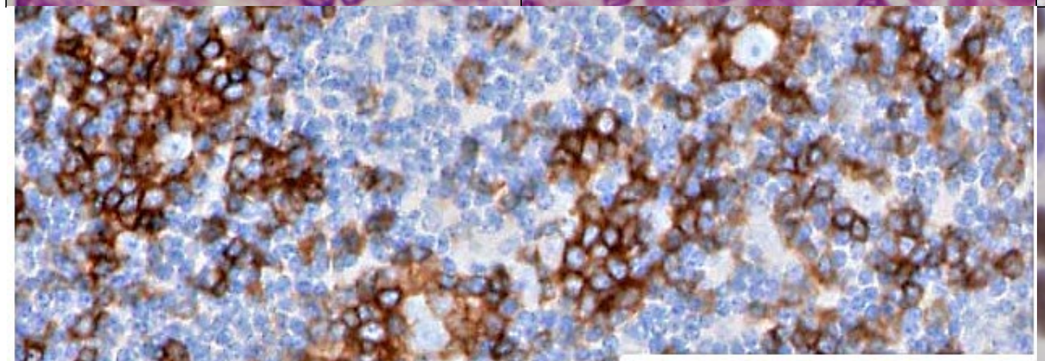


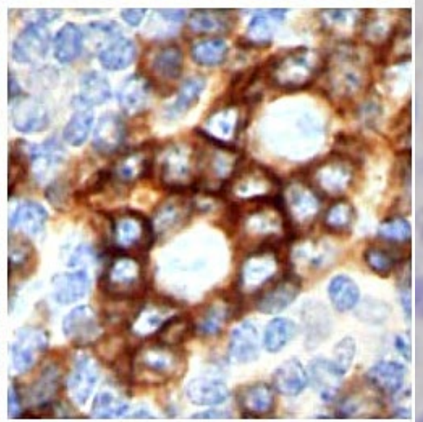


L&H cells

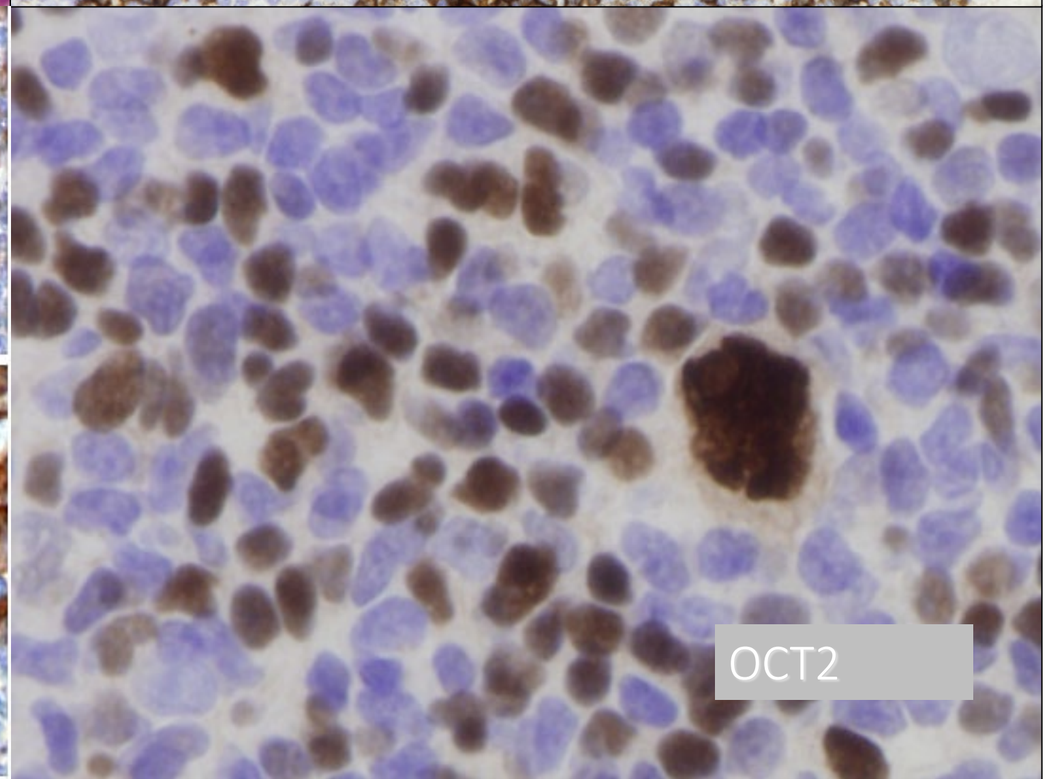


CD20





PD1



OCT2

Characterization of Variant Patterns of Nodular Lymphocyte Predominant Hodgkin Lymphoma with Immunohistologic and Clinical Correlation

Zhen Fan, MD, Yasodha Natkunam, MD, PhD, Eric Bair, BS, MS, Robert Tibshirani, PhD, and Roger A. Warnke, MD

Abstract: Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) has traditionally been recognized as having two morphologic patterns, nodular and diffuse, and the current WHO definition of NLPHL requires at least a partial nodular pattern. Variant patterns have not been well documented. We analyzed retrospectively the

Key Words: lymphocyte predominance, lymphocyte predominant, diffuse, nodular, Hodgkin lymphoma, variant patterns, T-cell-rich B-cell lymphoma, diffuse large B-cell lymphoma, immunohistochemistry

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

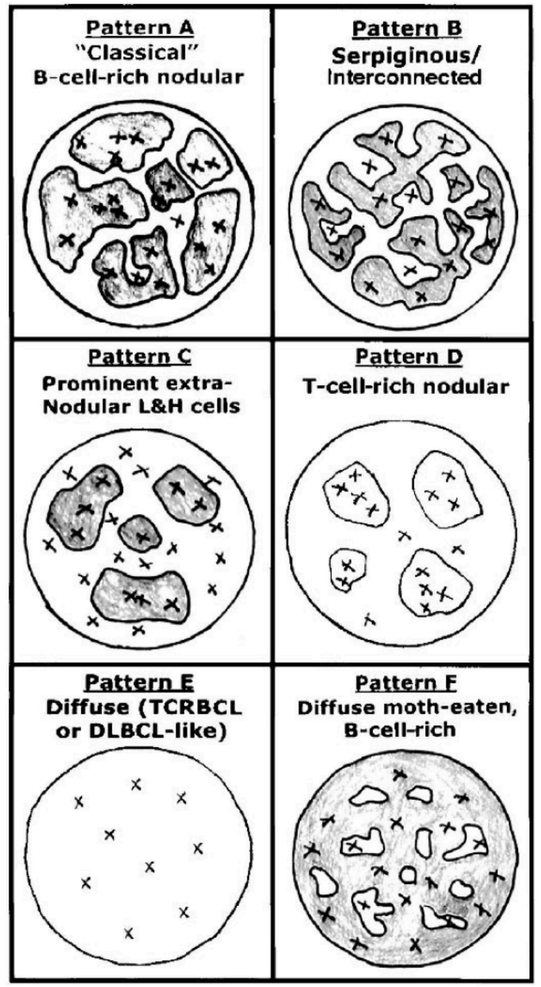


FIGURE 3. Immunoarchitectural patterns in NLPHL in schematic form (X: L&H cells, gray background; B-cell-rich background, blank/white background; T-cell-rich background). A, "Classic" B-cell-rich nodular pattern. B, Serpiginous nodular pattern. C, Nodular pattern with many extranodular L&H cells. D,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

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BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Treatment patterns and outcomes in adolescents and young adults with nodular lymphocyte-predominant Hodgkin lymphoma: an IMPACT cohort study

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Summary

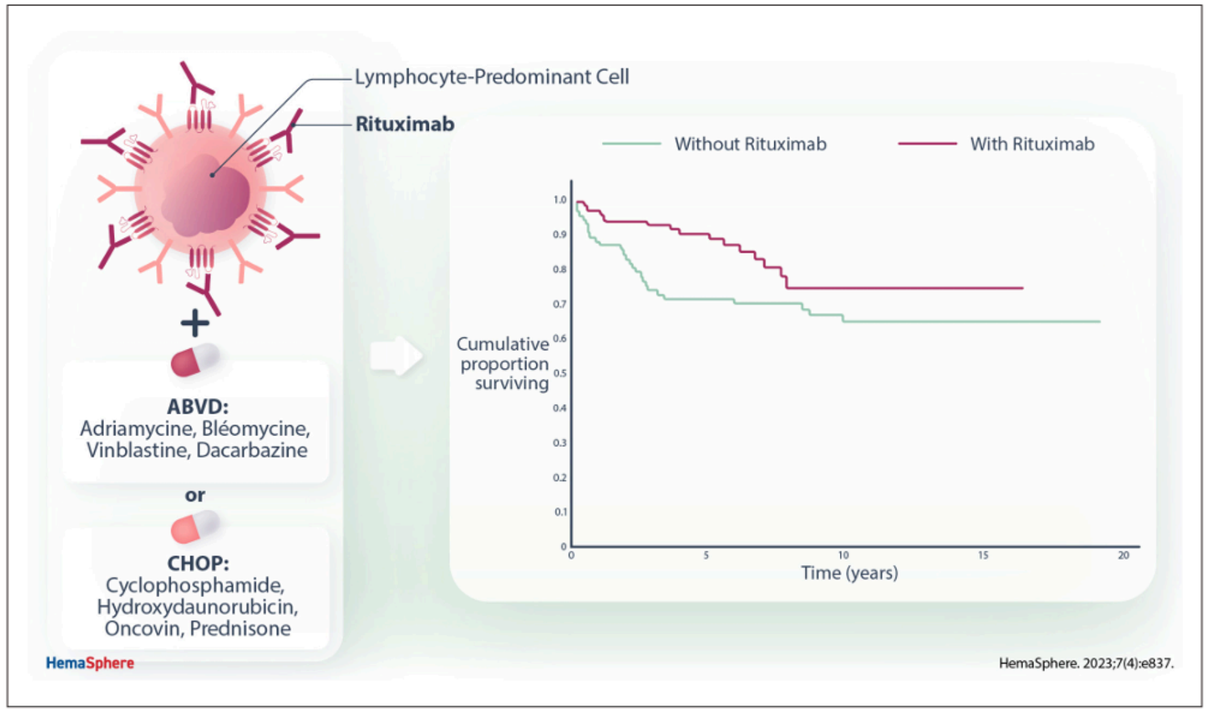
We leveraged population-based clinical and healthcare data to identify treatment patterns and long-term outcomes among adolescents and young adults (AYA) with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). All Ontario, Canada, AYA aged 15–21 years at diagnosis with NLPHL between 1992 and 2012 were identified, and their detailed clinical data were collected. Linkage to healthcare databases identified additional events (subsequent malignant neoplasms [SMN], relapses and deaths). Event-free survival (EFS) and overall survival (OS) were compared by locus of care (adult vs. paediatric) and predictors of outcomes determined. Of 1014 AYA with Hodgkin lymphoma, 54 (5.3%) had NLPHL; 15 (27.8%) were treated at a paediatric centre. No paediatric centre patient received radiation only versus 16 (41.0%) of adult centre patients. Excision only was more common in paediatric centres ($p < 0.001$). The 20-year EFS and OS rates were 82.9% ± 5.2% and 100% respectively. Advanced stage (hazard ratio: 4.9, 95% CI: 1.3–18.4; $p = 0.02$) was associated with inferior EFS. Although the 25-year cumulative incidence of SMN was 19.3% ± 9.6% for the entire cohort, there were no SMN among the patients treated with excision only. AYA with NLPHL have outstanding long-term survival. Resection alone was rare outside of paediatric institutions but associated with excellent outcomes. Given substantial SMN risks, chemotherapy-sparing and radiation-sparing strategies for appropriate subsets of patients are warranted.

Article
Open Access

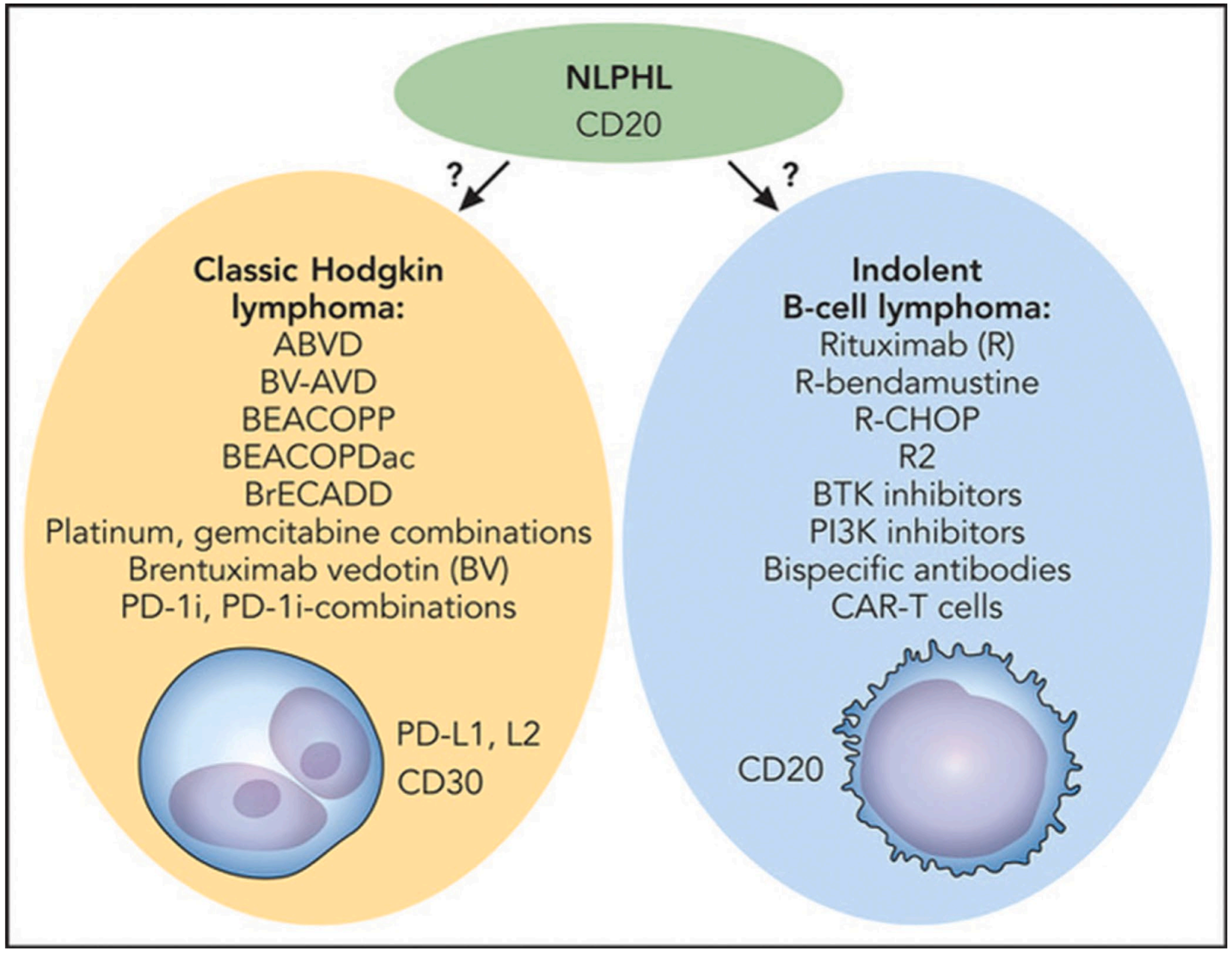
Role of Rituximab Addition to First-line Chemotherapy Regimens in Nodular Lymphocyte-predominant Hodgkin Lymphoma: A Study by Fondazione Italiana Linfomi

Manuel Gotti[1], Roberta Sciarra[1,2], Alessandro Pulsoni[3], Francesco Merli[4], Stefano Luminari[4,5], Caterina Zerbi[2], Livio Trentin[6], Alessandro Re[7], Chiara Rusconi[8], Simonetta Viviani[8,*], Andrea Rossi[9], Federica Cocito[10], Barbara Botto[11], Erika Meli[12], Antonello Pinto[13], Irene Dogliotti[14,*], Guido Gini[15], Benedetta Puccini[16], Francesca Ricci[17], Luca Nassi[18,*], Alberto Fabbri[19], Anna Marina Liberati[20], Michele Merli[21], Andrea Riccardo Filippi[22,23], Maurizio Bonfichi[1], Valentina Zoboli[1], Germana Tartaglia[3], Giorgia Annechini[3], Gianna Maria D'Elia[3], Ilaria Del Giudice[3], Isabel Alvarez[4], Andrea Visentin[6], Stefano Pravato[6], Daniela Dalceggio[7], Chiara Pagani[7], Silvia Ferrari[9], Caterina Cristinelli[2], Tanja Lazic[2], Virginia Valeria Ferretti[24], Umberto Ricardi[25], Luca Arcaini[1,2]

GRAPHICAL ABSTRACT



NLPHL: a hummingbird in an owl's nest



Daniel Molin, NLPHL: a hummingbird in an owl's nest, Blood, 2023,

frontiers | Frontiers in Oncology

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Microenvironmental immune cell alterations across the spectru of nodular lymphocyte predominant Hodgkin lymph and T-cell/histiocyte-rich lar B-cell lymphoma

Christos Panayi[1*], Ayse U. Akarca[2], Alan D. Ramsay[1], Ananth G. Shankar[3], Brunangelo Falini[4], Miguel A. Piris[5], David Linch[6] and Teresa Marafioti[1,2*]

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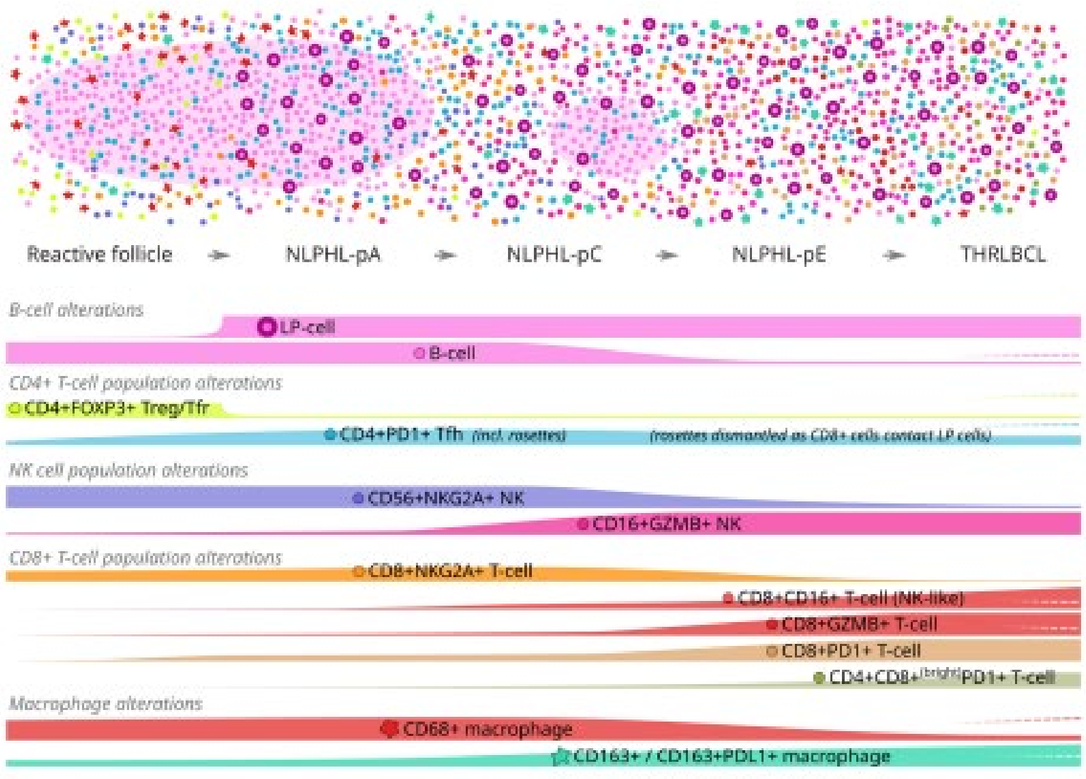
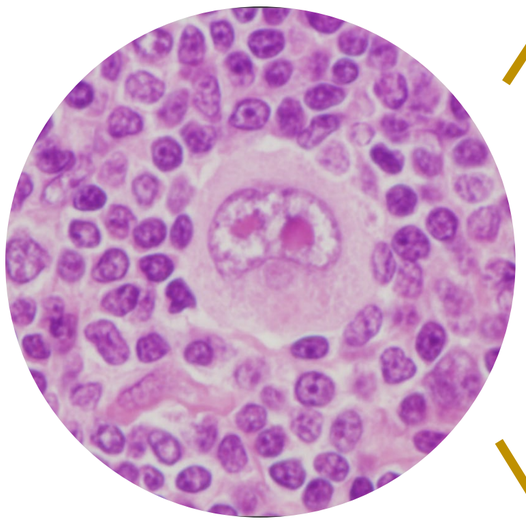


FIGURE 7
Graphical summary of differential microenvironmental phenotypic populations mapped to an idealised NLPHL/THRLBCL continuum. Illustration of cellular tumour composition (above) and phenotype mountain plots (below) for each phenotype of interest. Illustration key: light pink ovoids = B-cell rich nodules; cell phenotypes otherwise coloured/shaped as per icons in mountain plot labels. Mountain plots are illustrative only, based on relative findings between case types, and are not to scale; dashed lines (right) indicate the alternative alterations seen in the single "Treg-high" THRLBCL case.



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CD20
THRBCL progression

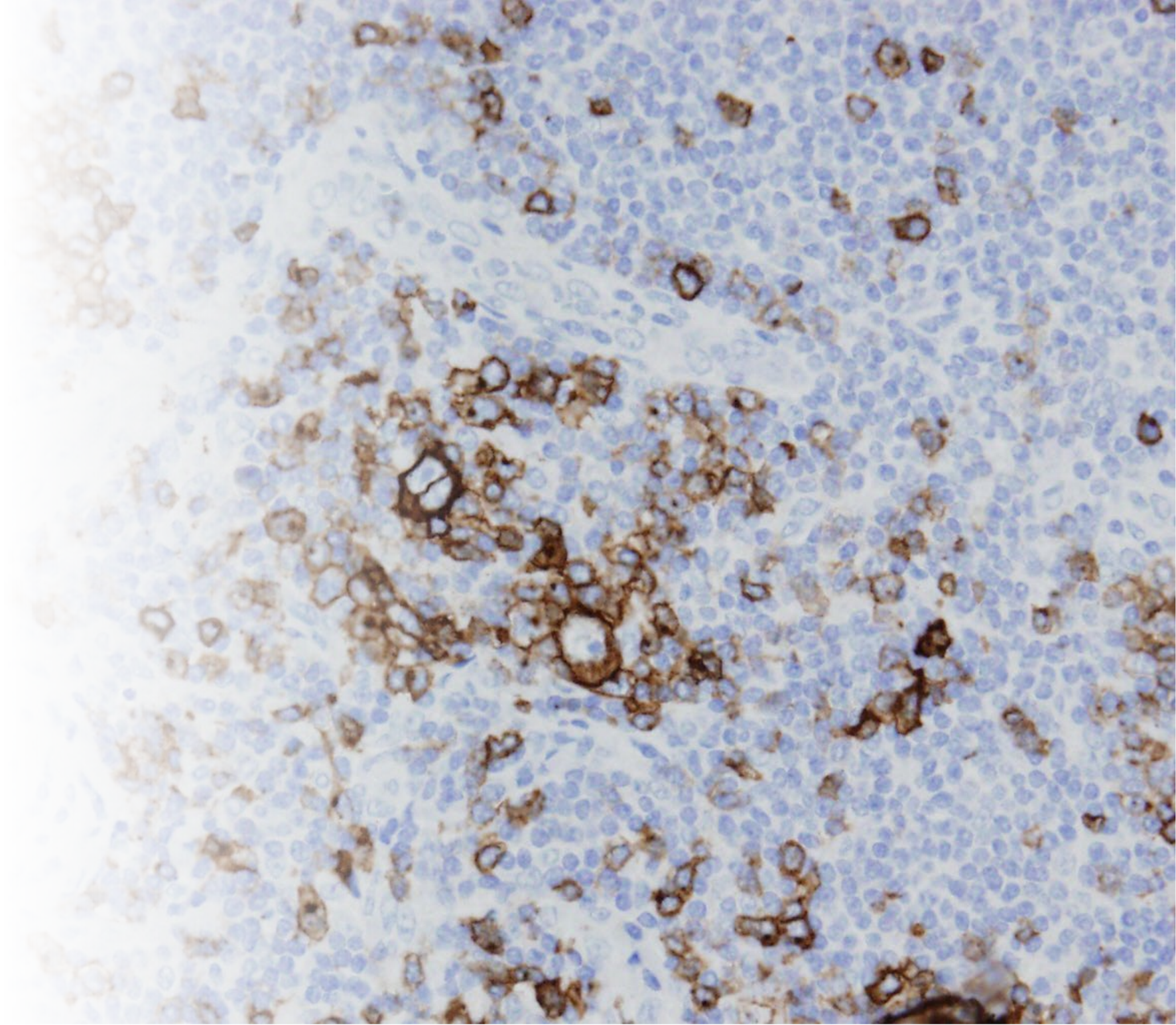
HRS Cells in
PTCL

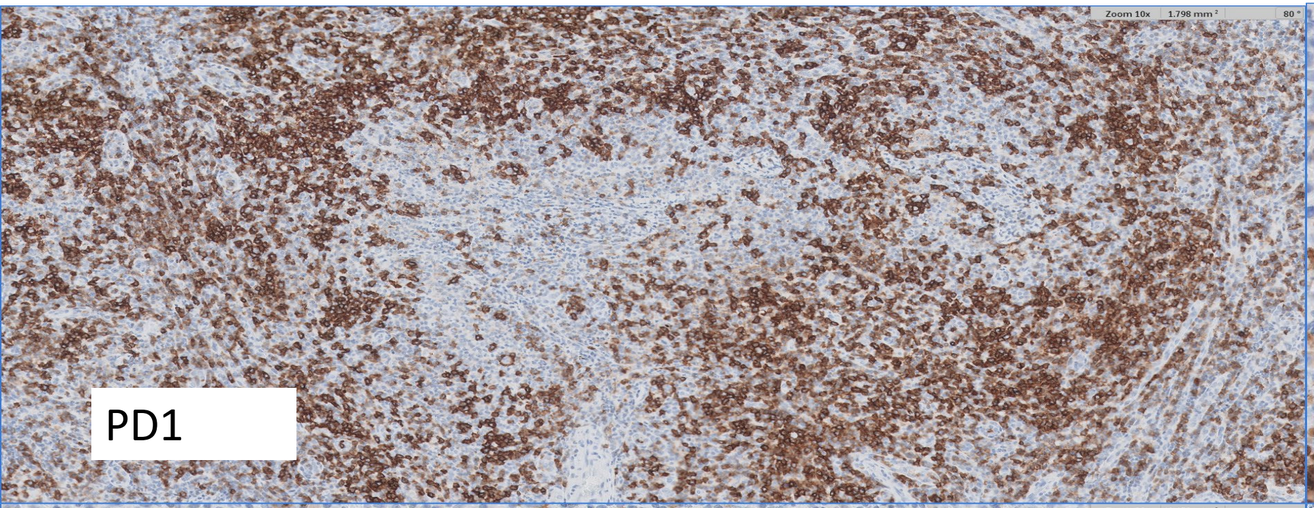
RHOA/IDH2 mt
TFH phenotype

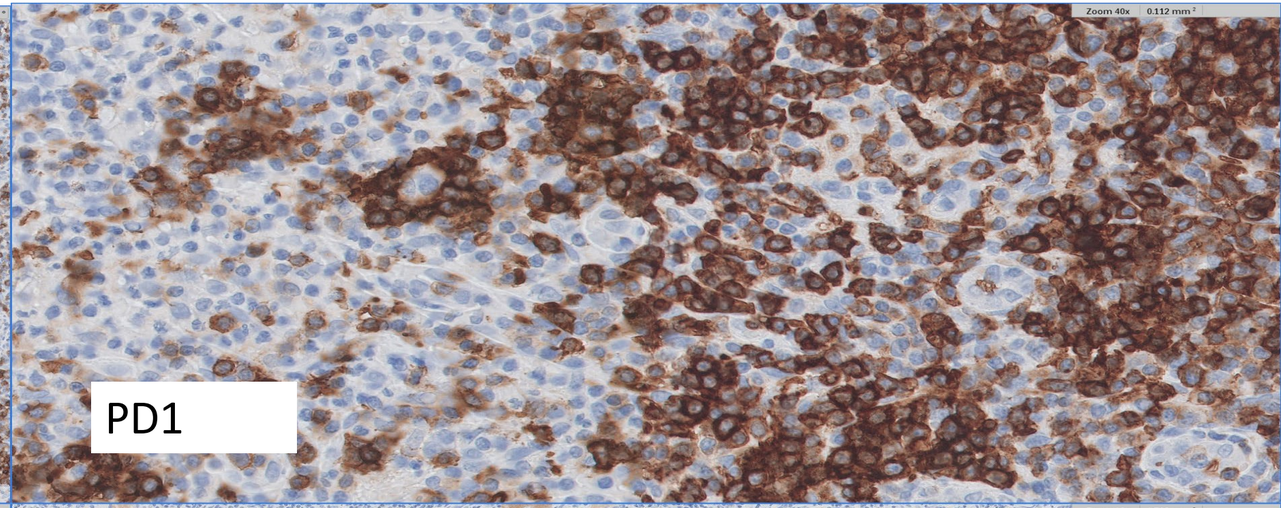
HRS cells in
BCL (EBV)

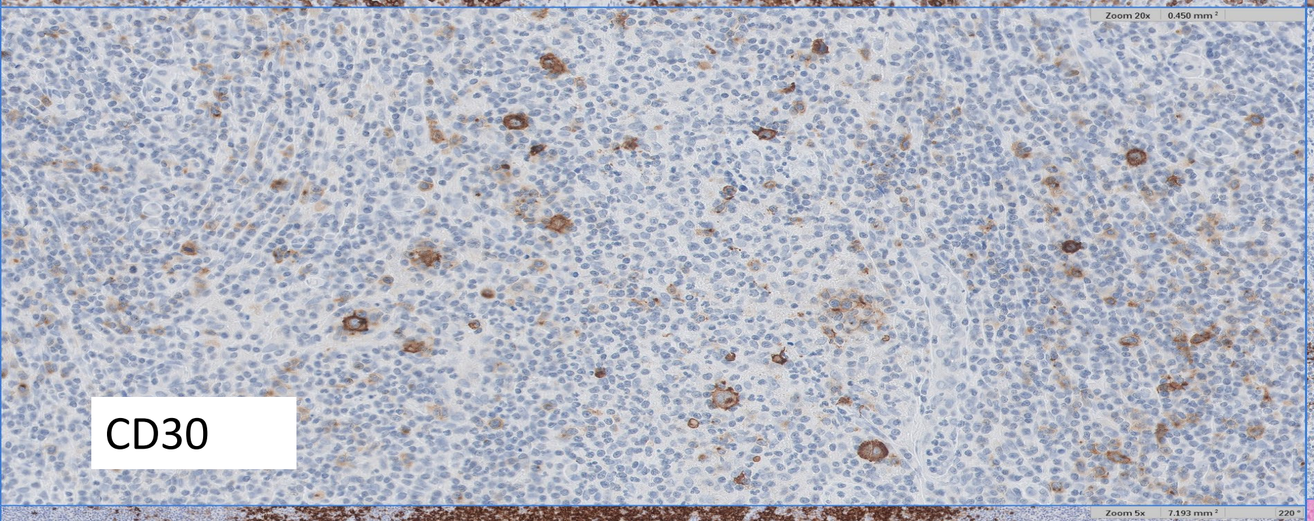
PTLD
EBV+ LBCL

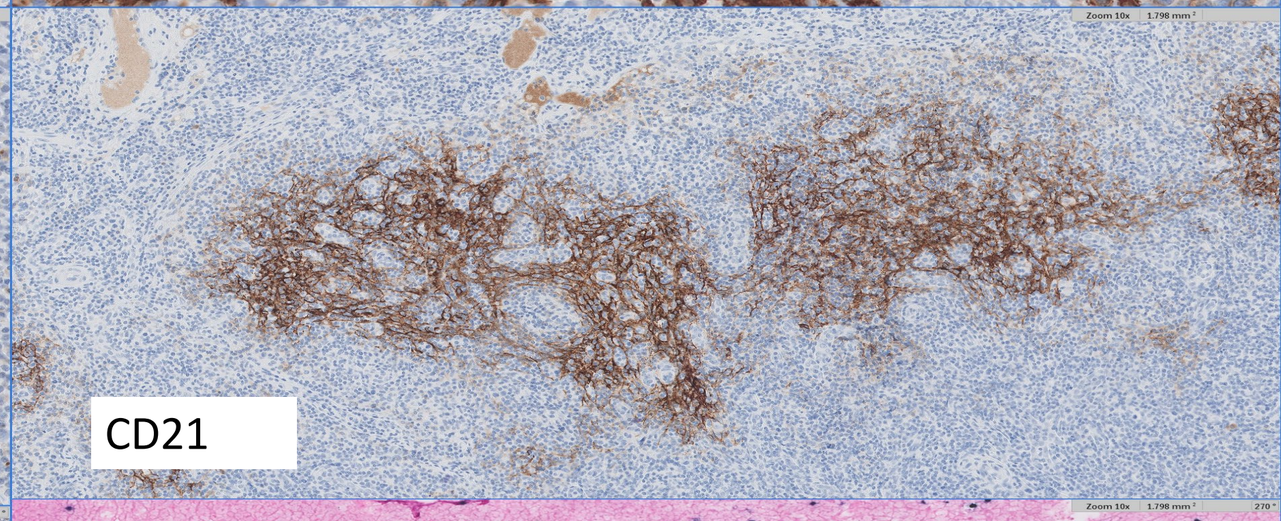
- CD30

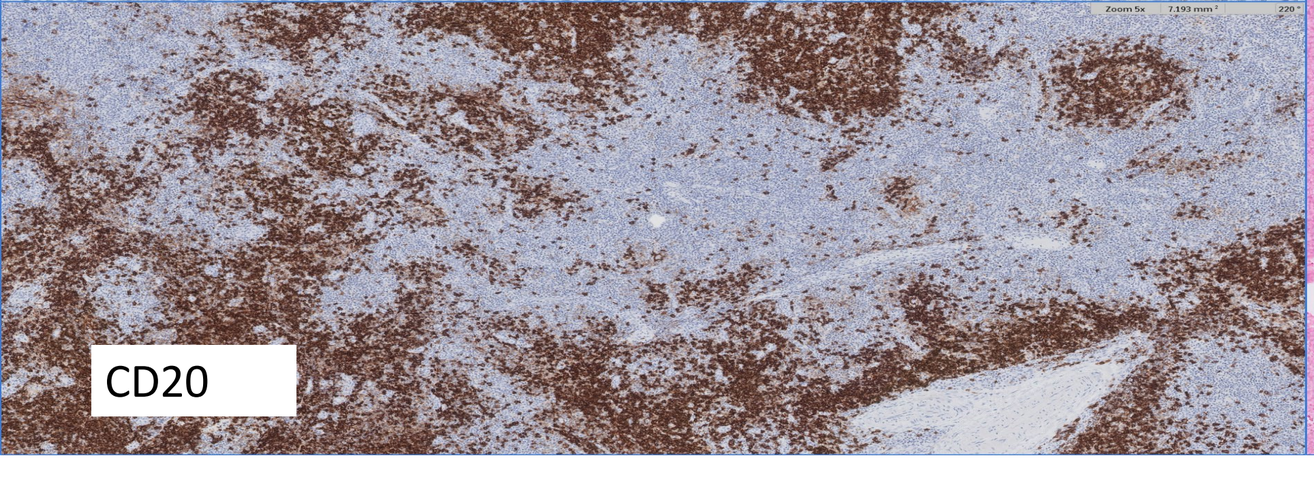


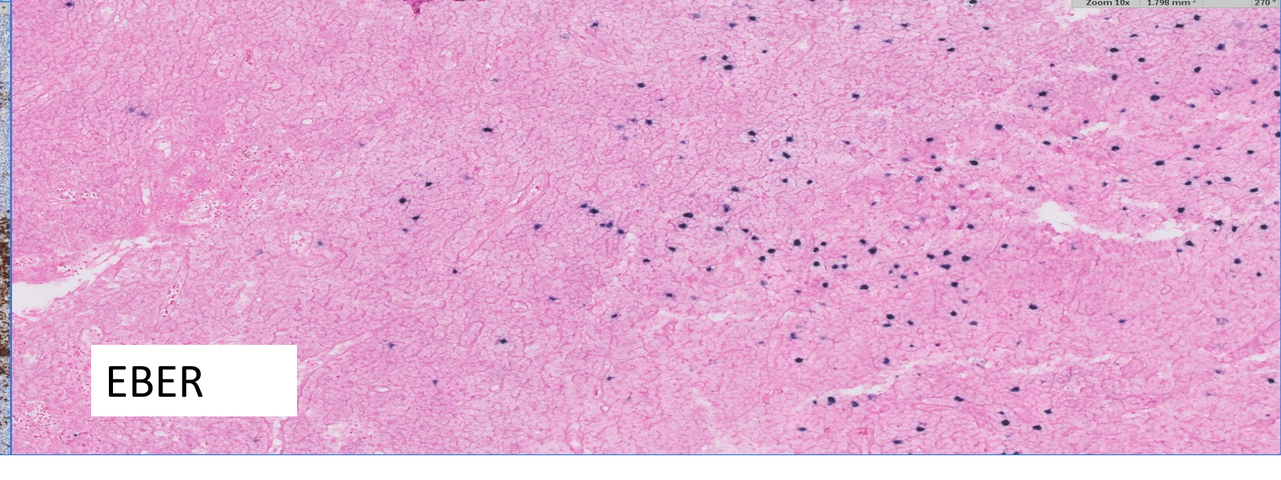

Zoom 10x 1.798 mm²
80 °
PD1


Zoom 40x 0.112 mm²
PD1


Zoom 20x 0.450 mm²
CD30


Zoom 10x 1.798 mm²
CD21


Zoom 5x 7.193 mm²
220 °
CD20


Zoom 10x 1.798 mm²
270 °
EBER

PTCL with CD30+ cells

ORIGINAL ARTICLE

Peripheral T-Cell Lymphomas Expressing CD30 and CD15

Todd S. Barry, MD, PhD, Elaine S. Jaffe, MD, Lynn Sorbara, PhD, Mark Raffeld, MD, and Stefania Pittaluga, MD, PhD

Peripheral T-Cell Lymphoma With Reed-Sternberg-like Cells of B-Cell Phenotype and Genotype Associated With Epstein-Barr Virus Infection

Leticia Quintanilla-Martinez, M.D., Falko Fend, M.D., Leticia Rodriguez Moguel, M.D., Lori Spilove, M.D., Michael W. Beaty, M.D., Douglas W. Kingma, M.D., Mark Raffeld, M.D., and Elaine S. Jaffe, M.D.

ORIGINAL ARTICLE

Nodal Involvement by Cutaneous CD30-positive T-cell Lymphoma Mimicking Classical Hodgkin Lymphoma

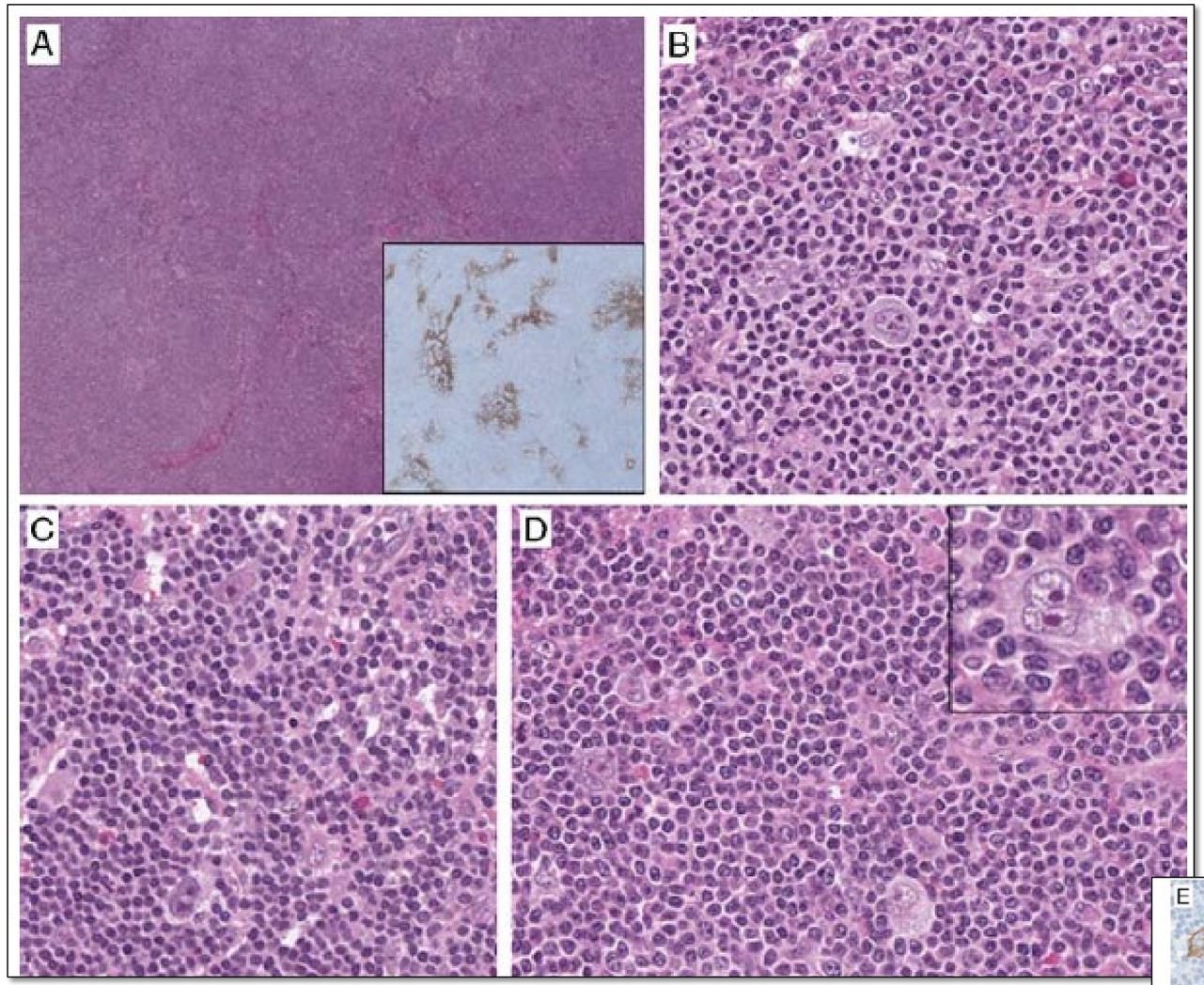
Franziska C. Eberle, MD, Joo Y. Song, MD,* Liqiang Xi, MD,* Mark Raffeld, MD,* Nancy Lee Harris, MD,† Wyndham H. Wilson, MD,‡ Stefania Pittaluga, MD, PhD,* and Elaine S. Jaffe, MD**

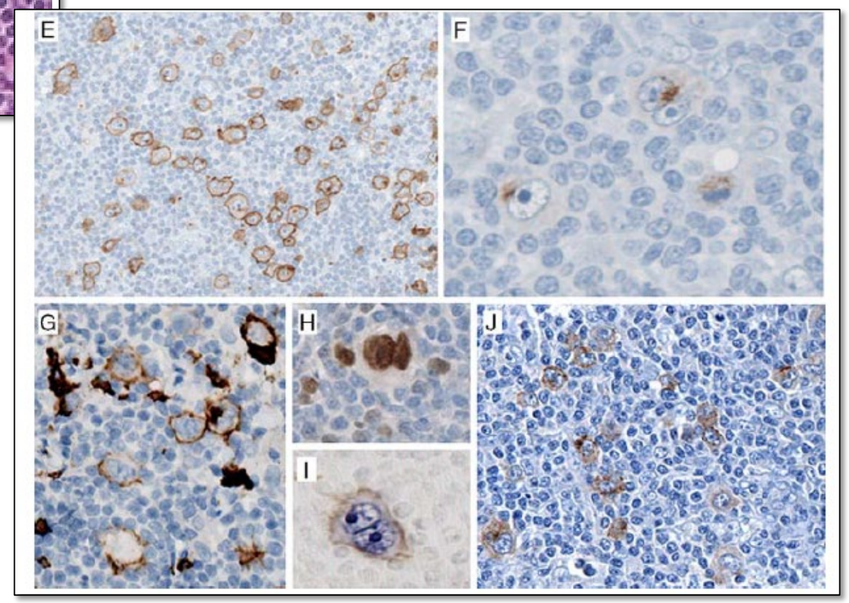
hybridization studies for Epstein Barr virus were negative. We show that cHL is less often associated with MF and primary cutaneous CD30-T-LPD than previously thought and that the coexpression of CD30 and CD15 in these TCLs may lead to a mistaken diagnosis of cHL.

TABLE 4. Prior Reports of Cutaneous TCL or CD30-T-LPD With cHL

References	# Cases	Skin Diagnosis	Extracutaneous Diagnosis	Sinusoidal Infiltration	Contiguous Nodal Involvement	*TRG* Performed on cHL Component
Chan et al[3]	3	MF	cHL, NS	NR	No (1), Yes (2)	ND
Simrell et al[21]	1	MF	cHL, NS	No	NR	ND
Kaudewitz et al[11]	2	LyP	cHL, MC	NR	No (2)	ND
Davis et al[4]	1	MF, LyP	cHL, MC, ALCL	Yes	No	Clonal*
Brousset et al[2]	2	MF	cHL, NS	NR	NR	Polyclonal
Kadin et al[9]	1	CD30-T-LPD	cHL, NS	Yes	Yes	Clonal*
Kremer et al[12]	1	MF	cHL†	NR	NR	Polyclonal
Willenbrock et al[27]	1	CD30-T-LPD	cHL, MC	No	NR	Clonal*
Gellrich et al[8]	1	LyP	cHL	NR	NR	ND‡

*Identical clone in lymph node and skin.
†Bone marrow involvement.
‡Clonal by *IG* gene rearrangement.
ALCL indicates anaplastic large cell lymphoma; CHL, classical Hodgkin lymphoma; MC, mixed cellularity subtype; ND, not done; NR, not reported; NS, nodular sclerosis subtype; *TRG*, T-cell receptor gene rearrangement.





ORIGINAL ARTICLE

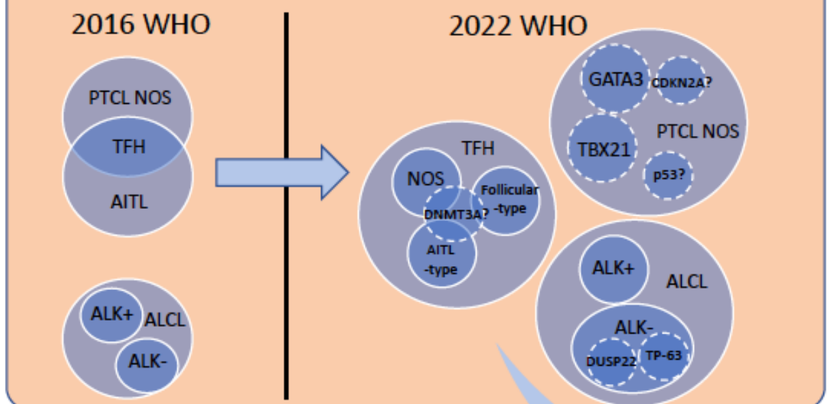
Follicular Peripheral T-cell Lymphoma Expands the Spectrum of Classical Hodgkin Lymphoma Mimics

Julien Moroch, MD,† Christiane Copie-Bergman, MD, PhD,*†‡ Laurence de Leval, MD, PhD,§ Anne Plonquet, MD,†‡‖ Nadine Martin-Garcia, BSc,†‡ Marie-Hélène Delfau-Larue, MD, PhD,†‡‖ Valérie Molinier-Frenkel, MD, PhD,†‡‖ Karim Belhadj, MD,¶ Corinne Haioun, MD,†¶ Josée Audouin, MD,# Steven H. Swerdlow, MD,** Teresa Marafioti, MD, PhD,†‡†† and Philippe Gaulard, MD*†‡*

Treatment of the common nodal peripheral T-cell lymphomas (PTCLs) is evolving

The "common" nodal peripheral T-cell lymphomas (PTCLs), which include PTCL, not otherwise specified (PTCL, NOS), the T-follicular helper (TFH) lymphomas, and anaplastic large cell lymphomas (ALCL) have typically been associated with poor outcomes and their rarity pose challenges for conducting clinical trials and understanding biology. Recent studies have highlighted important differences among these diseases with respect to cell of origin or cell state, genetic profile, and drug sensitivity; however, up until recently, these diseases were treated similarly.

Improved Classification

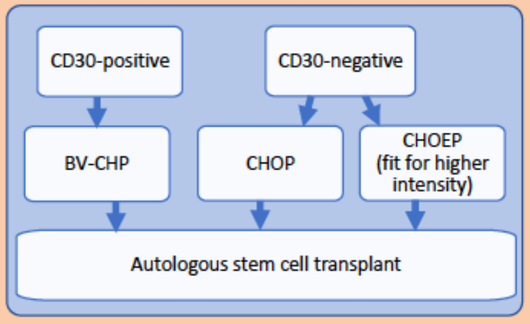


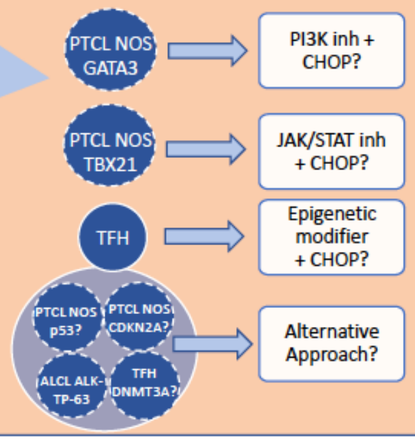
New Targets and Drugs

Targeted Agents	Epigenetic Modifying Agents	Pathway Inhibitor
CD30 ALK PD-1 CD94 Bispecific CD30/CD16 PD-1/CD3	HDACi Belinostat Romidepsin Chidamide Azacytidine Valemetostat Enasidinib	PI3K-kinase JAK/STAT

Current Treatments and Potential Directions

Current front-line treatment





Future treatment of the common peripheral T-cell lymphomas will recognize the numerous distinct entities and thoughtfully incorporate novel agents to optimize therapy for each individual.

blood

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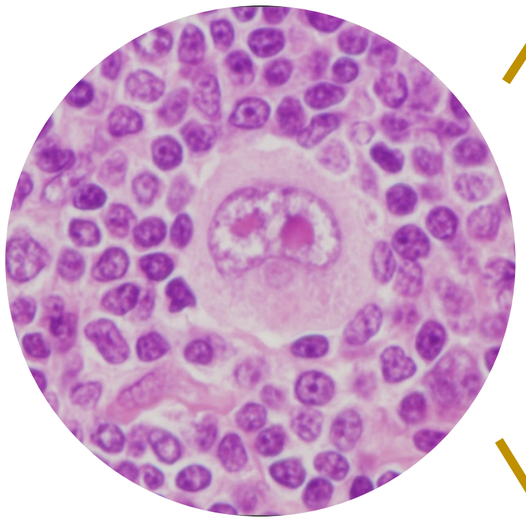
editorial@hematology.org

Current and upcoming treatment approaches to common subtypes of PTCL (PTCL NOS, ALCL, TFHs)

Tracking no: BLD-2023-021789-CR1

Alison Moskowitz (Memorial Sloan Kettering Cancer Center, United States) Robert Stuver (Memorial Sloan Kettering Cancer Center, United States) Steven Horwitz (Memorial Sloan Kettering Cancer Center, United States)



NSCHL

CD30
9p24,…
STAT6 mt,…
Mediastinal Grey Zone

Lymphocyte predominance

NLPBL

GC BCL
OCT2/TFH rosettes
CD20
THRBCL progression

HRS Cells in

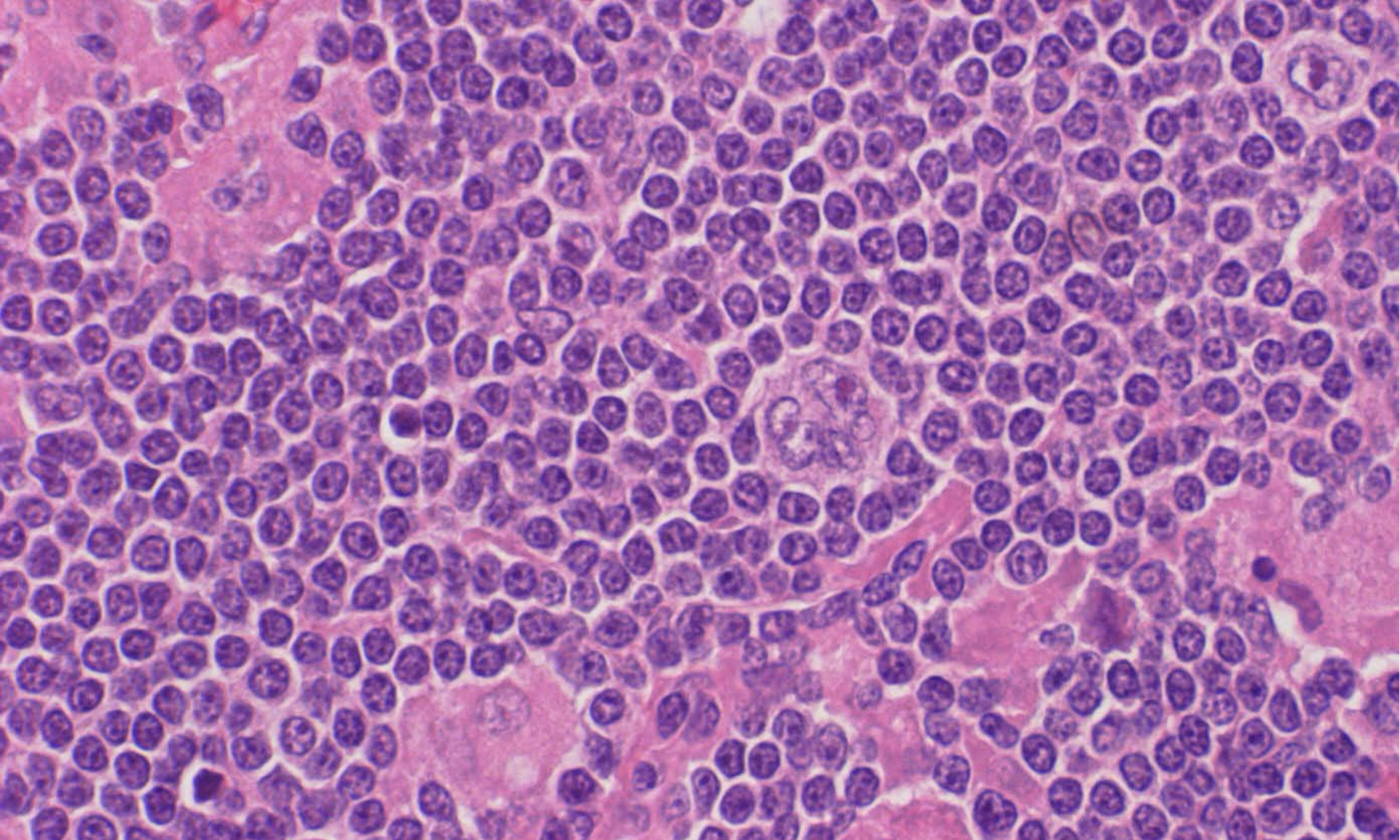
PTCL

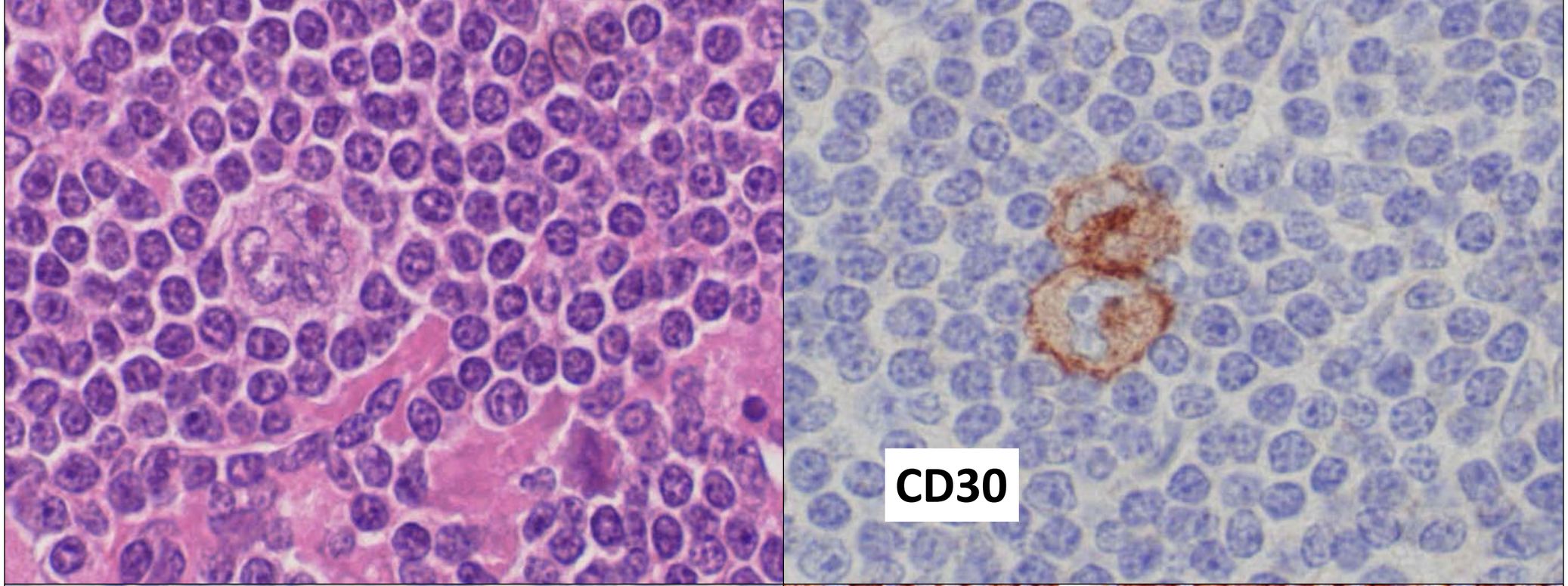
RHOA/IDH2 mt
TFH phenotype

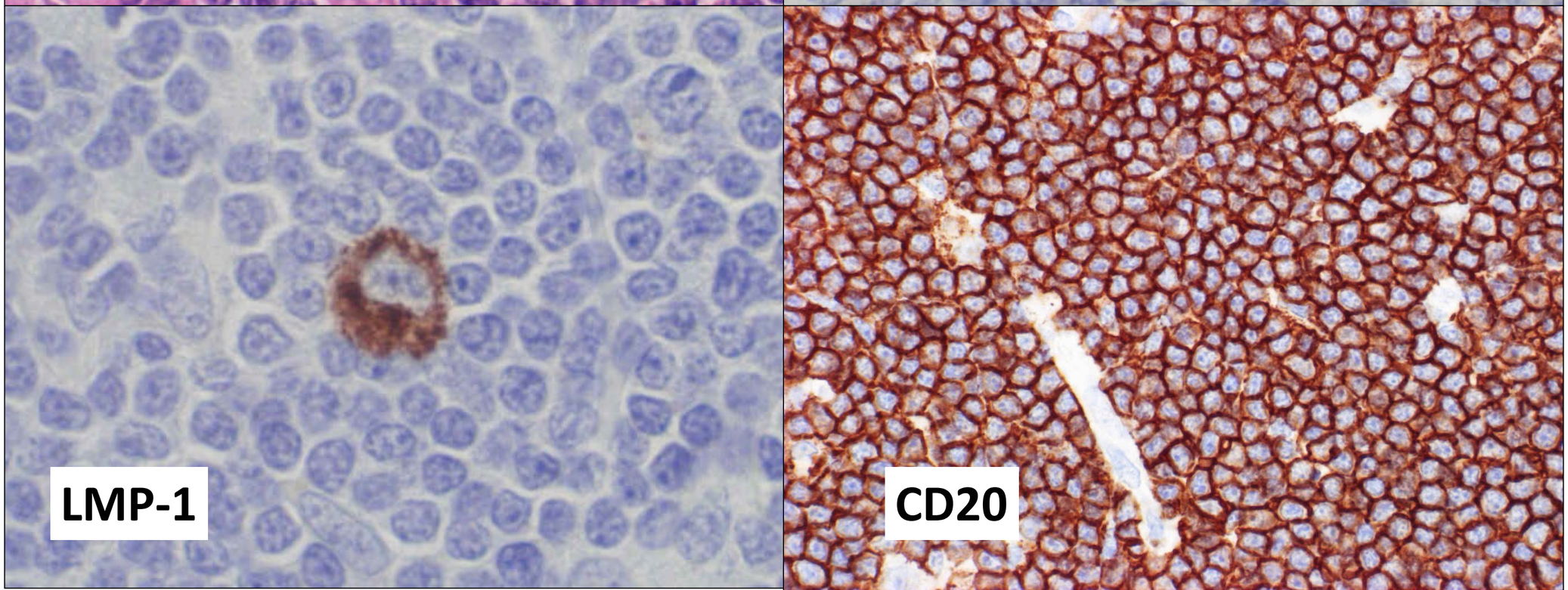
HRS cells in

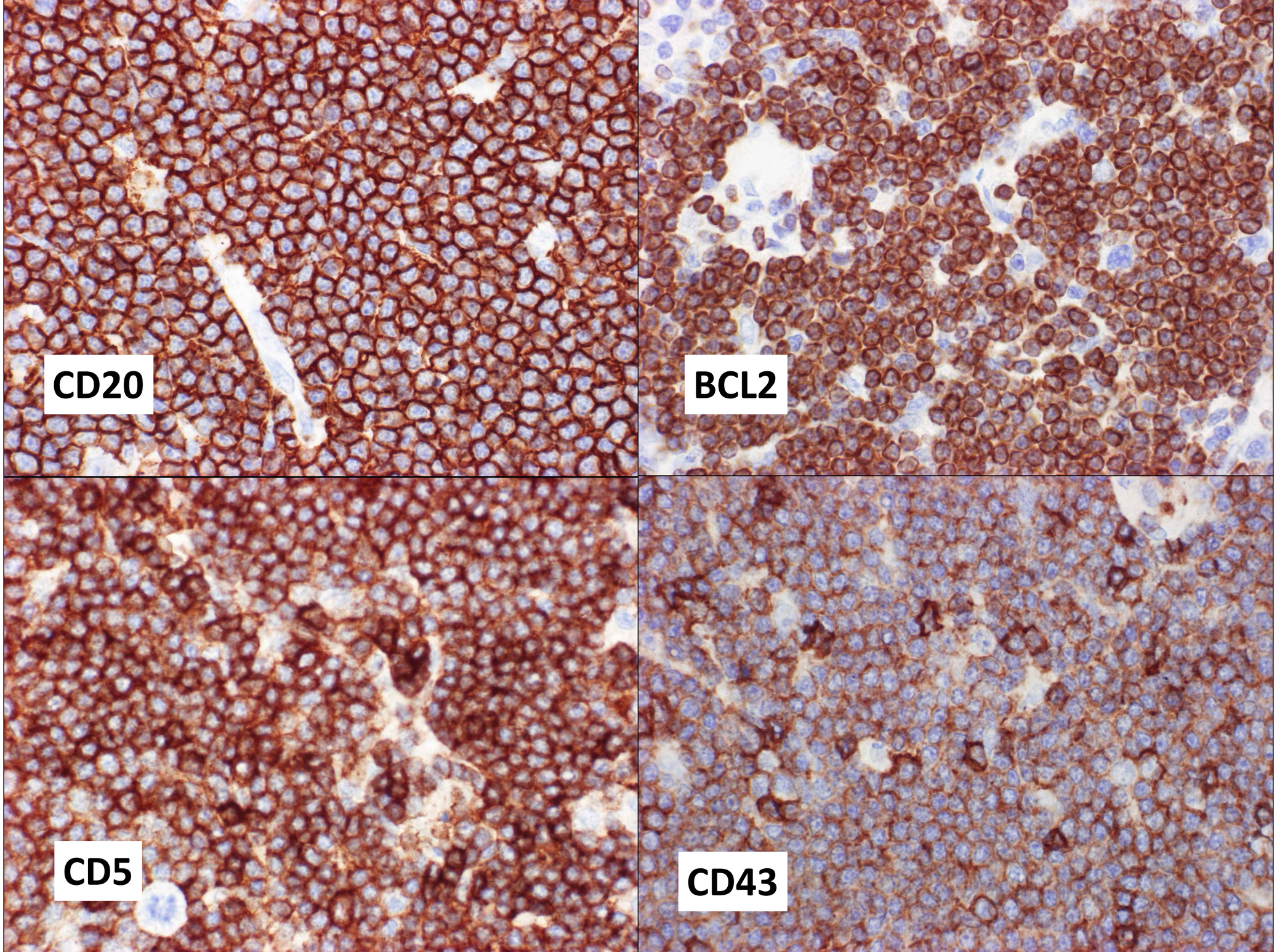
BCL (EBV)

PTLD
EBV+ LBCL

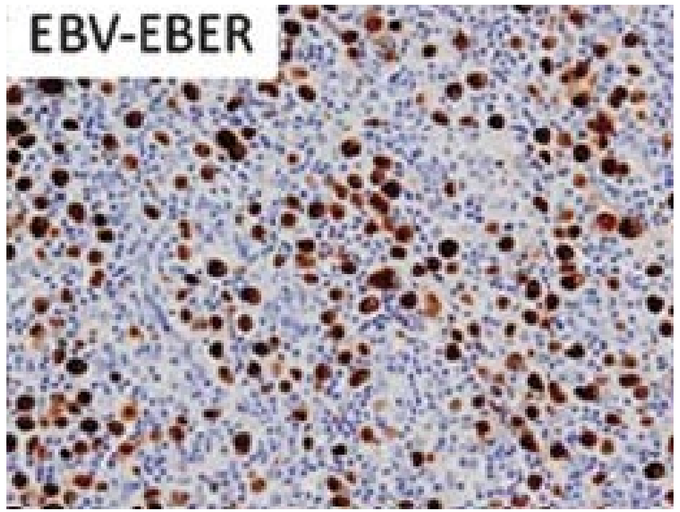


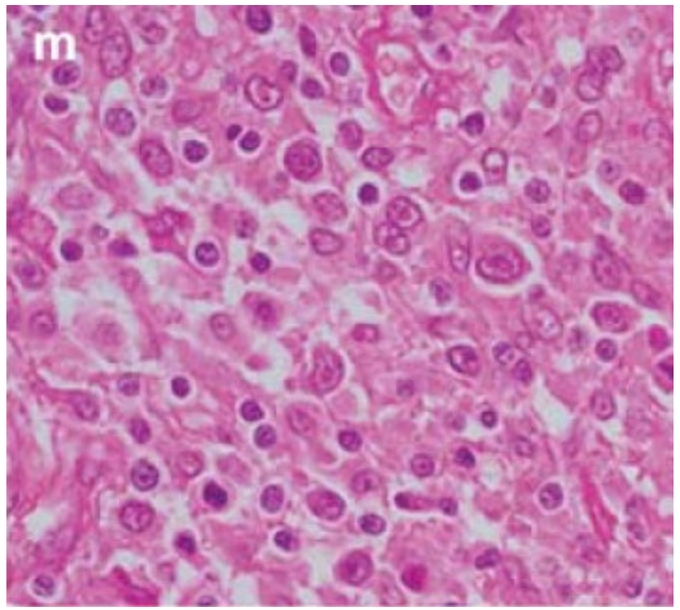

CD30


LMP-1
CD20


CD20
BCL2
CD5
CD43

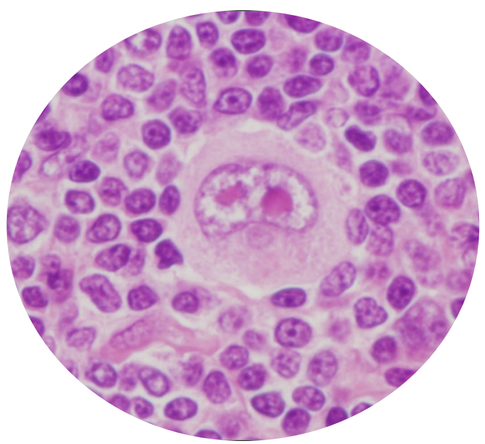
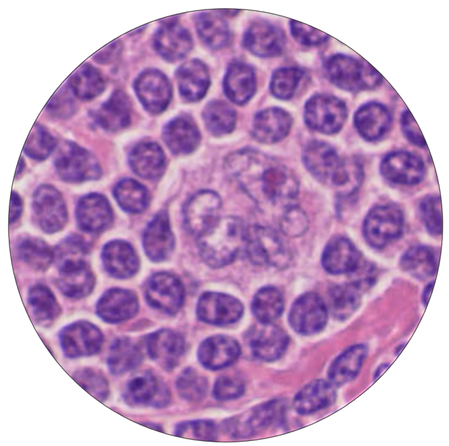
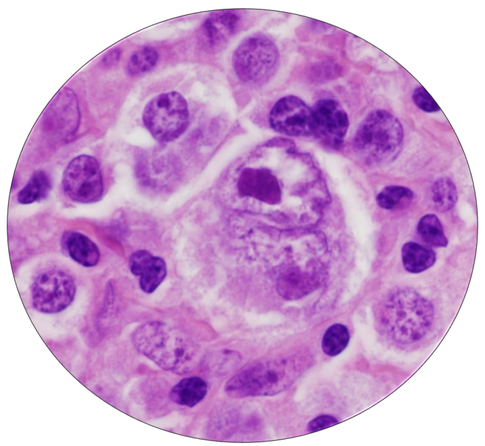
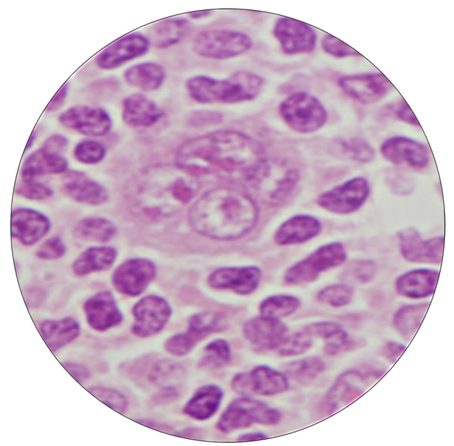
EBV+ DLBCL





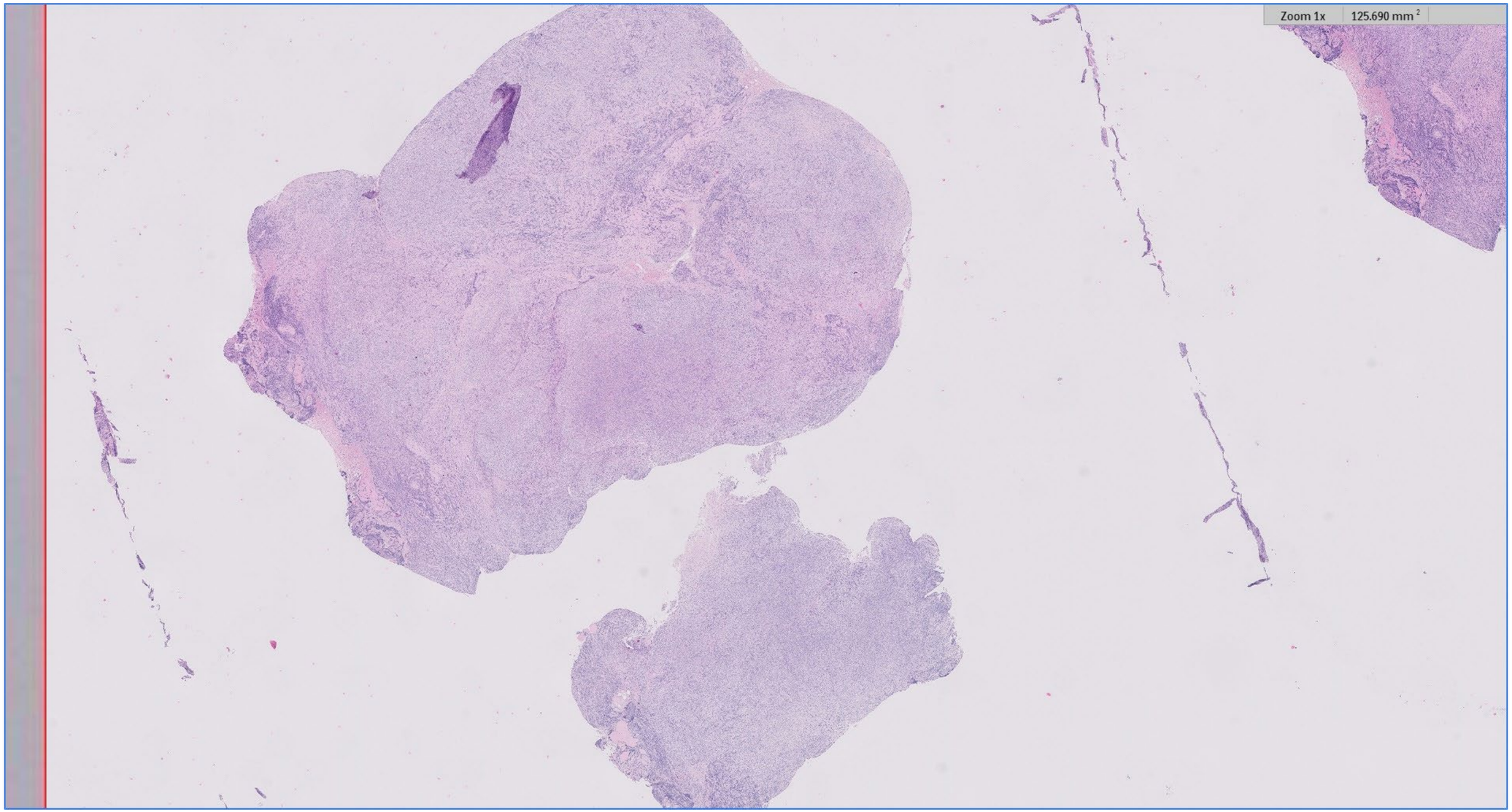
- Primary
- No apparent immunodeficiency
- More advanced stage and age
- More than one extranodal involvement
- Higher IPI risk group with poor response to initial treatment
- Variable polymorpic infiltrate
- The differential diagnosis with EBV-positive classic Hodgkin Lymphoma (CHL) can be challenging; however, expression of B-cell markers in >50% of the tumor cells, extranodal presentation, and/or EBV latency III favors the diagnosis of EBV-positive DLBCL, NOS. Extended B-cell antibody panels are critical in this setting.
- EBV+ large cell lymphoma are excluded from this category, if
  - Associated with chronic inflammation
  - LyG, PBL, PEL

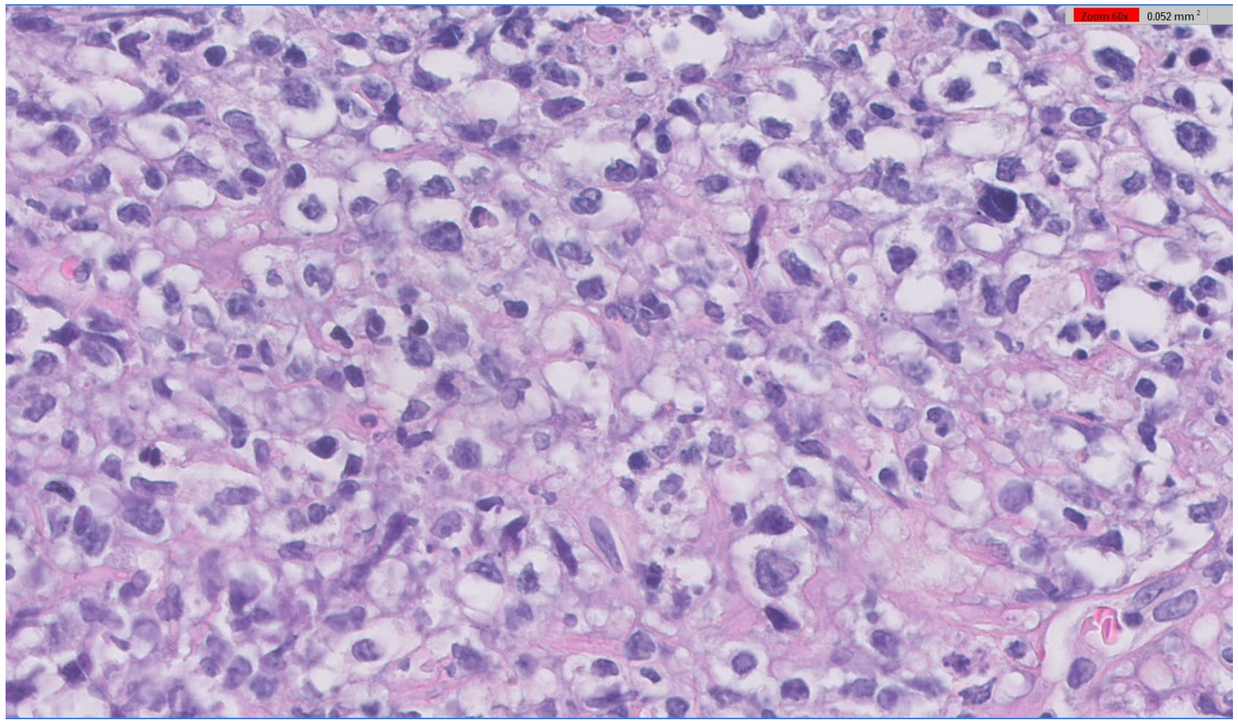
- SR cells with CD30+ CD15+ EBV/LMP+ phenotype can be seen in different conditions
- Molecular background underlying this phenotype in Non-Hodgkin LPDs merits further research
- Role of the expression of STAT6 and 9p24 genes (PDL1, PDL2, JAK2)[iii]
- Classical HL cases could represent an heterogenous disorder

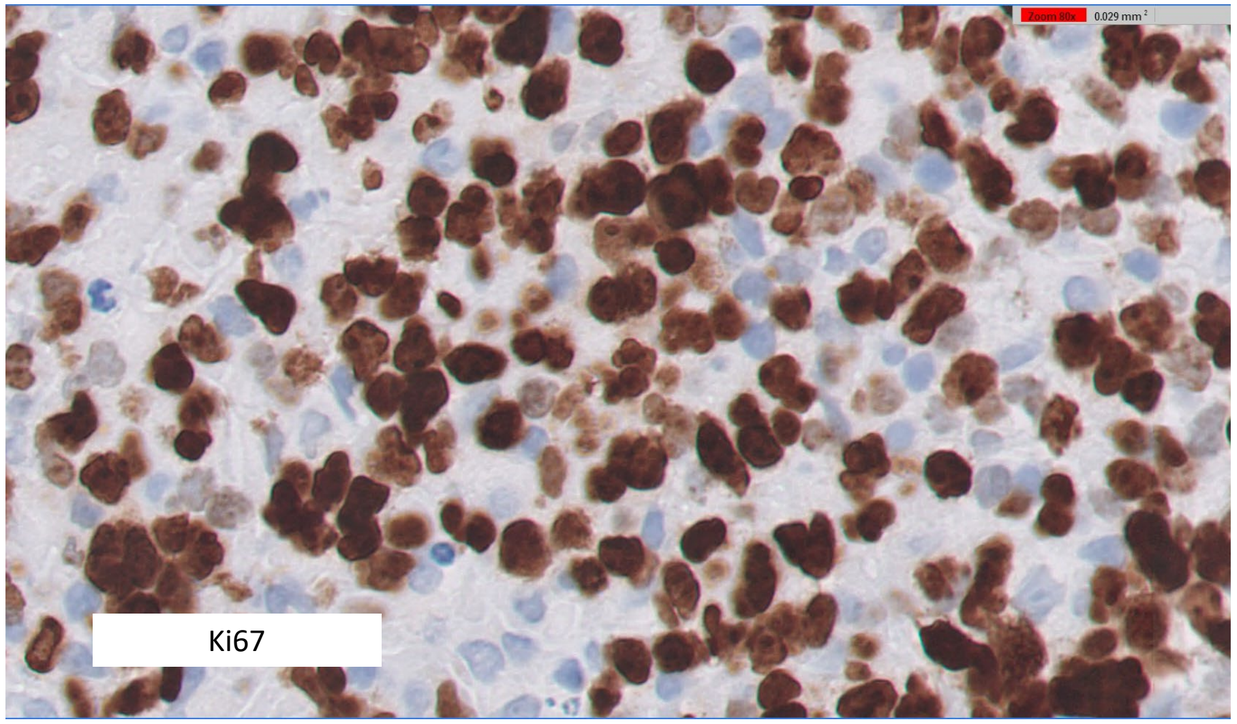





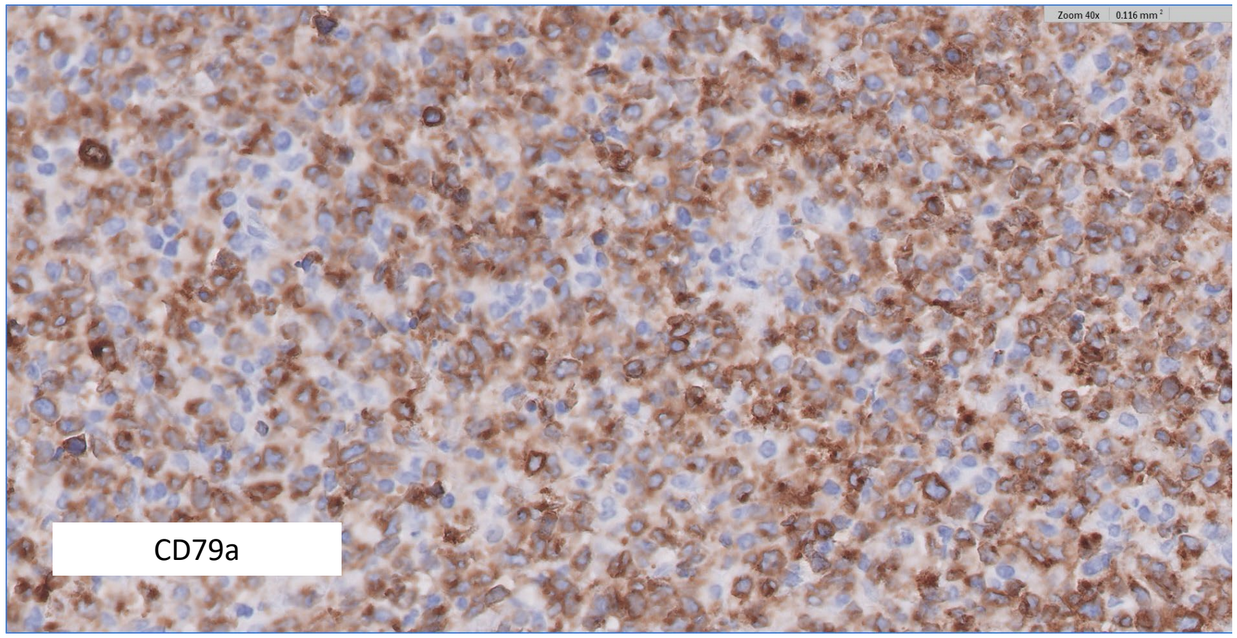
25 yrs male

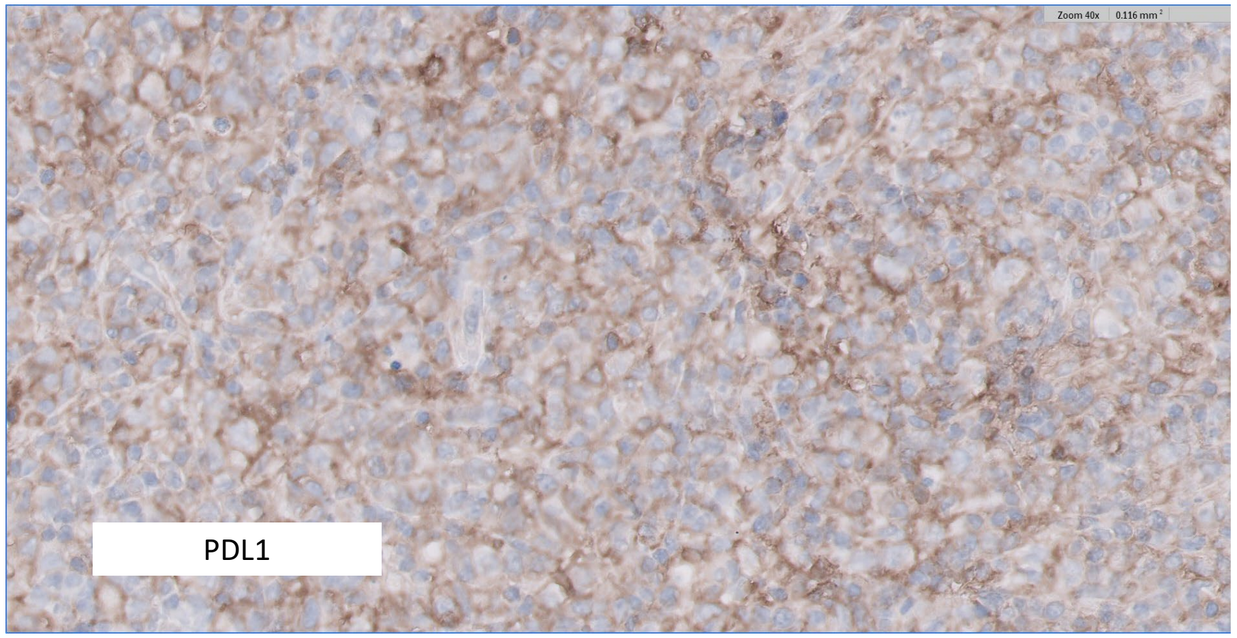
Anterior mediastinal mass


Zoom 1x
125.690 mm ²




Ki67


CD79a


PDL1

IHC

B-cell markers:	PMLBCL markers:	Others:
• Positive for PAX5 and CD79a • Negative for CD20	• Positive for CD23, PDL1, PDL2 • Negative for STAT6 • Minimal CD30 expression	• BCL6 positive • CD15 negative • MUM1, MYC, BCL2 intermediate expression • High Ki67

Differential

- Diffuse LBCL
- Primary mediastinal LBCL
- Hodgkin Lymphoma
- Mediastinal gray zone

- B2M: NM_004048; chr15:45003779; exon 1; c.35T>C; p.Leu12Pro (missense; VAF=31.9%)
- B2M: NM_004048; chr15:45007650; c.99_130del; p.His33Glnfs*13 (frameshift; VAF=21%)
- IRF4: NM_001195286; chr6:394899; exon 3; c.295T>C; p.Cys99Arg (missense; VAF=35.2%)
- SOCS1: NM_003745; chr16:11348882; exon 2; c.452_454delinsCGC; p.Leu151_Glu152delinsProGln (missense; VAF=33.4%)
- ARID1A: NM_006015; chr1:27058039; exon 3; c.1747C>T; p.Gln583* (nonsense; VAF=29.9%)
- NFKBIE: NM_004556; chr6:44232738; exon 1; c.759_762del; p.Tyr254Serfs*13 (frameshift; VAF=32.8%)
- NFKBIE: NM_004556; chr6:44227956; exon 5; c.1261C>T; p.Gln421* (nonsense; VAF=34.3%)
- CIITA: NM_000246; chr16:11001691; exon 11; c.2342_2345delinsTGGC; p.Ser781_Val782delinsLeuAla (missense; VAF=21.9%)
- 9p24 amplification

LYMPHOID NEOPLASIA

Integrative genomic analysis identifies key pathogenic mechanisms in primary mediastinal large B-cell lymphoma

Anja Mottok,[1-3,*] Stacy S. Hung,[1,*] Elizabeth A. Chavez,[1] Bruce Woolcock,[1] Adèle Telenius,[1] Lauren C. Chong,[1] Barbara Meissner,[1] Hisae Nakamura,[1] Christopher Rushton,[4] Elena Viganò,[1] Clementine Sarkozy,[1] Randy D. Gascoyne,[1,2] Joseph M. Connors,[1] Susana Ben-Neriah,[1] Andrew Mungall,[5] Marco A. Marra,[5] Reiner Siebert,[3] David W. Scott,[1] Kerry J. Savage,[1] and Christian Steidl[1,2]

[1]British Columbia Cancer, Centre for Lymphoid Cancer, Vancouver, BC, Canada; [2]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; [3]Institute of Human Genetics, Ulm University and Ulm University Medical Center, Ulm, Germany; [4]Department of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, BC, Canada; and [5]British Columbia Cancer, Canada's Michael Smith Genome Sciences Centre, Vancouver, BC, Canada

KEY POINTS

- **Whole-exome sequencing and gene expression profiling reveal genetic driver alterations and elucidate pathway dependencies in PMBL.**
- **Comparative analysis points to relevant differences to diffuse large B-cell lymphoma and highlights the pathological and molecular relatedness to cHL.**

Primary mediastinal large B-cell lymphoma (PMBL) represents a clinically and pathologically distinct subtype of large B-cell lymphomas. Furthermore, molecular studies, including global gene expression profiling, have provided evidence that PMBL is more closely related to classical Hodgkin lymphoma (cHL). Although targeted sequencing studies have revealed a number of mutations involved in PMBL pathogenesis, a comprehensive description of disease-associated genetic alterations and perturbed pathways is still lacking. Here, we performed whole-exome sequencing of 95 PMBL tumors to inform on oncogenic driver genes and recurrent copy number alterations. The integration of somatic gene mutations with gene expression signatures provides further insights into genotype–phenotype interrelation in PMBL. We identified highly recurrent oncogenic mutations in the Janus kinase-signal transducer and activator of transcription and nuclear factor κB pathways, and provide additional evidence of the importance of immune evasion in PMBL (*CIITA*, *CD58*, *B2M*, *CD274*, and *PDCD1LG2*). Our analyses highlight the interferon response factor (IRF) pathway as a putative novel hallmark with frequent alterations in multiple pathway members (*IRF2BP2*, *IRF4*, and *IRF8*). In addition, our integrative analysis illustrates the importance of *JAK1*, *RELB*, and *EP300* mutations driving oncogenic signaling. The identified driver genes were significantly more frequently mutated in PMBL compared with diffuse large B-cell lymphoma, whereas only a limited number of genes were significantly different between PMBL and cHL, emphasizing the close relation between these entities. Our study, performed on a large cohort of PMBL, highlights the importance of distinctive genetic alterations for disease taxonomy with relevance for diagnostic evaluation and therapeutic decision-making. (*Blood*. 2019;134(10):802-813)

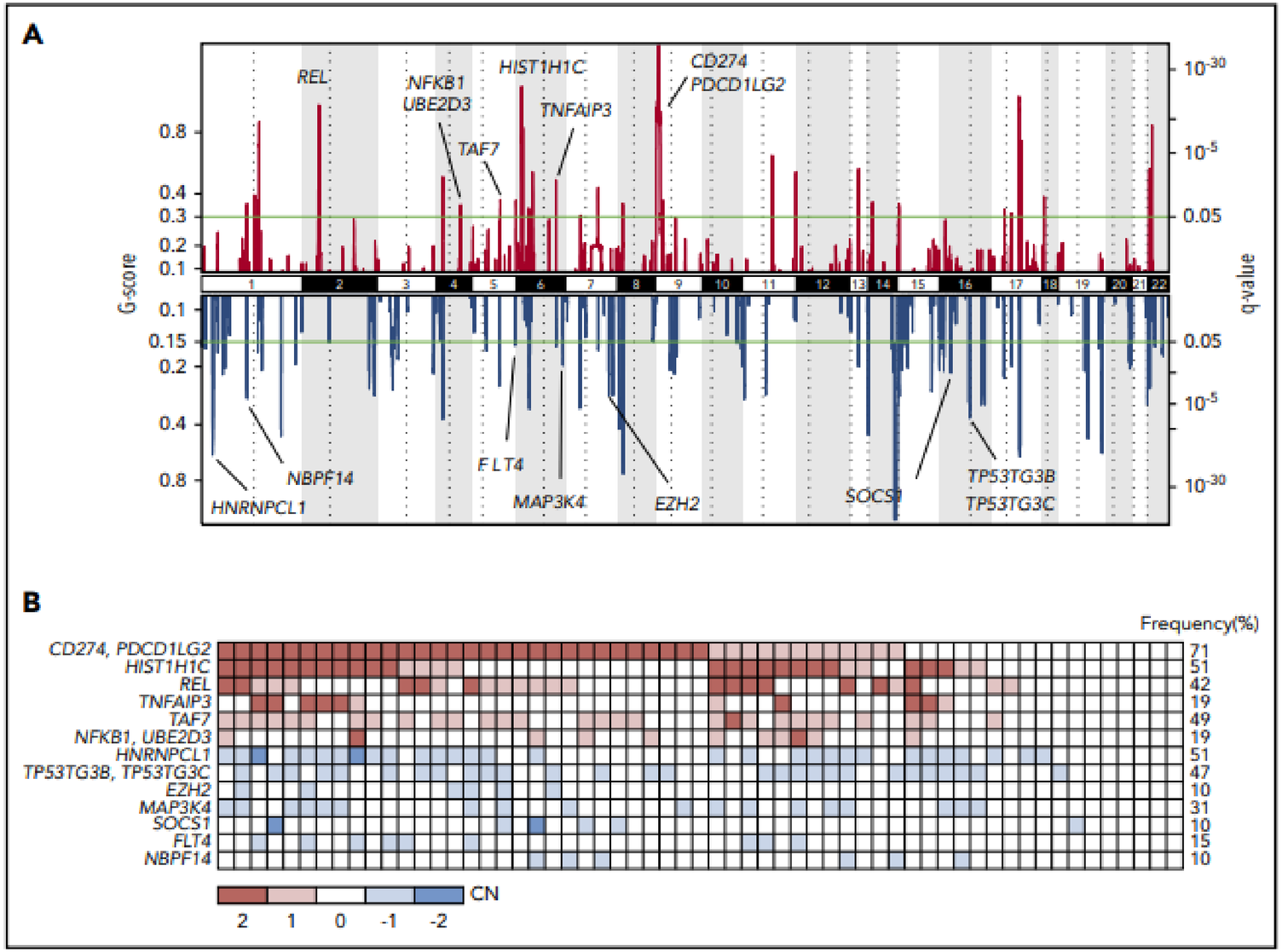
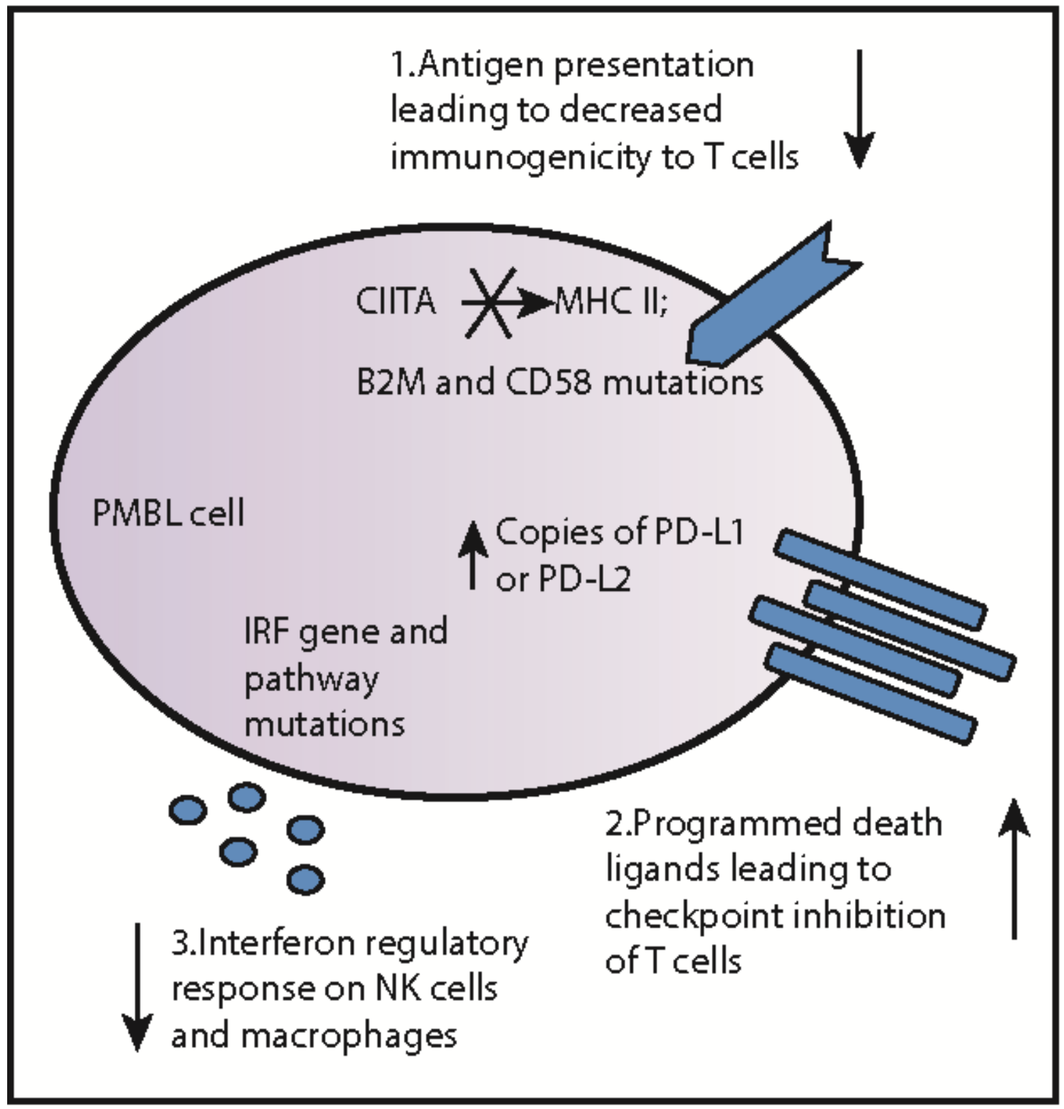


Figure 3. Recurrent CN alterations in PMBL. (A) Significant CN gains (red) and losses (blue) as inferred from whole-exome sequencing data using GISTIC 2.0. Potential candidate genes are highlighted next to their respective genomic locus. (B) Frequency plot of genes displaying significant CN alterations across the cohort. Red indicates CN gain, and blue indicates CN loss, where values are derived from GISTIC and indicate copy-number level per gene: −2 = homozygous deletion; −1 = heterozygous deletion; 0 = CN unchanged; 1 = low-level gain; 2 = high-level gain/amplification. Genes were sorted according to gain/deletion and then per q value as calculated by using GISTIC.

PMBL: flying under the immune radar



Lisa M. Rimsza, PMBL: flying under the immune radar, Blood, 2019,

LYMPHOID NEOPLASIA

Mutational landscape of gray zone lymphoma

Clémentine Sarkozy,[1,2] Stacy S. Hung,[1] Elizabeth A. Chavez,[1] Gerben Duns,[1] Katsuyoshi Takata,[1] Lauren C. Chong,[1] Tomohiro Aoki,[1] Aixiang Jiang,[1] Tomoko Miyata-Takata,[1] Adèle Telenius,[1] Graham W. Slack,[1] Thierry Jo Molina,[3] Susana Ben-Neriah,[1] Pedro Farinha,[1] Peggy Dartigues,[4] Diane Damotte,[5,6] Anja Mottok,[7] Gilles A. Salles,[2,8] Rene-Olivier Casasnovas,[9] Kerry J. Savage,[1] Camille Laurent,[10] David W. Scott,[1] Alexandra Traverse-Glehen,[2,11] and Christian Steidl[1]

[1]Centre for Lymphoid Cancer, British Columbia Cancer, Vancouver, BC, Canada; [2]INSERM Unité Mixte de Recherche (UMR) S1052, Centre National de la Recherche UMR 5286, Centre de Recherche en Cancérologie de Lyon, Lyon, France; [3]Pathology Department, Necker Enfants Malades Hospital, Université Paris Descartes, Assistance Publique–Hôpitaux de Paris (AP–HP), Paris, France; [4]Pathology Department, Gustave Roussy, Université Paris-Saclay, INSERM U1170, Villejuif, France; [5]Pathology Department, Groupe Hospitalier Cochin, AP-HP, Paris, France; [6]INSERM U1138, Paris Descartes University-Sorbonne Paris Cité, Paris, France; [7]Institute of Human Genetics, Ulm University and Ulm University Medical Center, Ulm, Germany; [8]Département d'Hématologie, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Pierre Bénite Cedex, France; [9]Department of Hematology, François Mitterrand University Hospital, INSERM U1231, Dijon, France; [10]Institut Universitaire du Cancer-Oncopole de Toulouse, CHU Toulouse, INSERM U1037, Centre de Recherche en Cancerologie de Toulouse-Purpan, Toulouse-Purpan, France; and [11]Département de Pathologie, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Pierre Bénite Cedex, France

KEY POINTS

- The mutational landscape of GZL in the thymic niche resembles that of EBV$^-$ cHL and PMBCL, suggesting a shared cell of origin.
- GZLs occurring outside of the thymic niche have a distinct mutational profile, with a subset of cases carrying *TP53* and *BCL2* mutations.

The mutational landscape of gray zone lymphoma (GZL) has not yet been established, and differences from related entities are largely unknown. Here, we studied coding sequence mutations of 50 Epstein-Barr virus (EBV)-negative GZLs and 20 polymorphic EBV$^+$ diffuse large B-cell lymphoma (DLBCL) not otherwise specified (poly-EBV-L) in comparison with classical Hodgkin lymphoma (cHL), primary mediastinal large B-cell lymphoma (PMBCL), and DLBCL. Exomes of 21 GZL and 7 poly-EBV-L cases, along with paired constitutional DNA, were analyzed as a discovery cohort, followed by targeted sequencing of 217 genes in an extension cohort of 29 GZL and 13 poly-EBV-L cases. GZL cases with thymic niche involvement (anterior mediastinal mass) exhibited a mutation profile closely resembling cHL and PMBCL, with *SOCS1* (45%), *B2M* (45%), *TNFAIP3* (35%), *GNA13* (35%), *LRRN3* (32%), and *NFKBIA* (29%) being the most recurrently mutated genes. In contrast, GZL cases without thymic niche involvement (n = 18) had a significantly distinct pattern that was enriched in mutations related to apoptosis defects (*TP53* [39%], *BCL2* [28%], *BIRC6* [22%]) and depleted in *GNA13*, *XPO1*, or NF-κB signaling pathway mutations (*TNFAIP3*, *NFKBIE*, *IKBKB*, *NFKBIA*). They also exhibited more *BCL2/BCL6* rearrangements compared with thymic GZL. Poly-EBV-L cases presented a distinct mutational profile, including *STAT3* mutations and a significantly lower coding mutation load in comparison with EBV$^-$ GZL. Our study highlights characteristic mutational patterns in GZL associated with presentation in the thymic niche, suggesting a common cell of origin and disease evolution overlapping with related anterior mediastinal lymphomas. (*Blood*. 2021;137(13):1765-1776)

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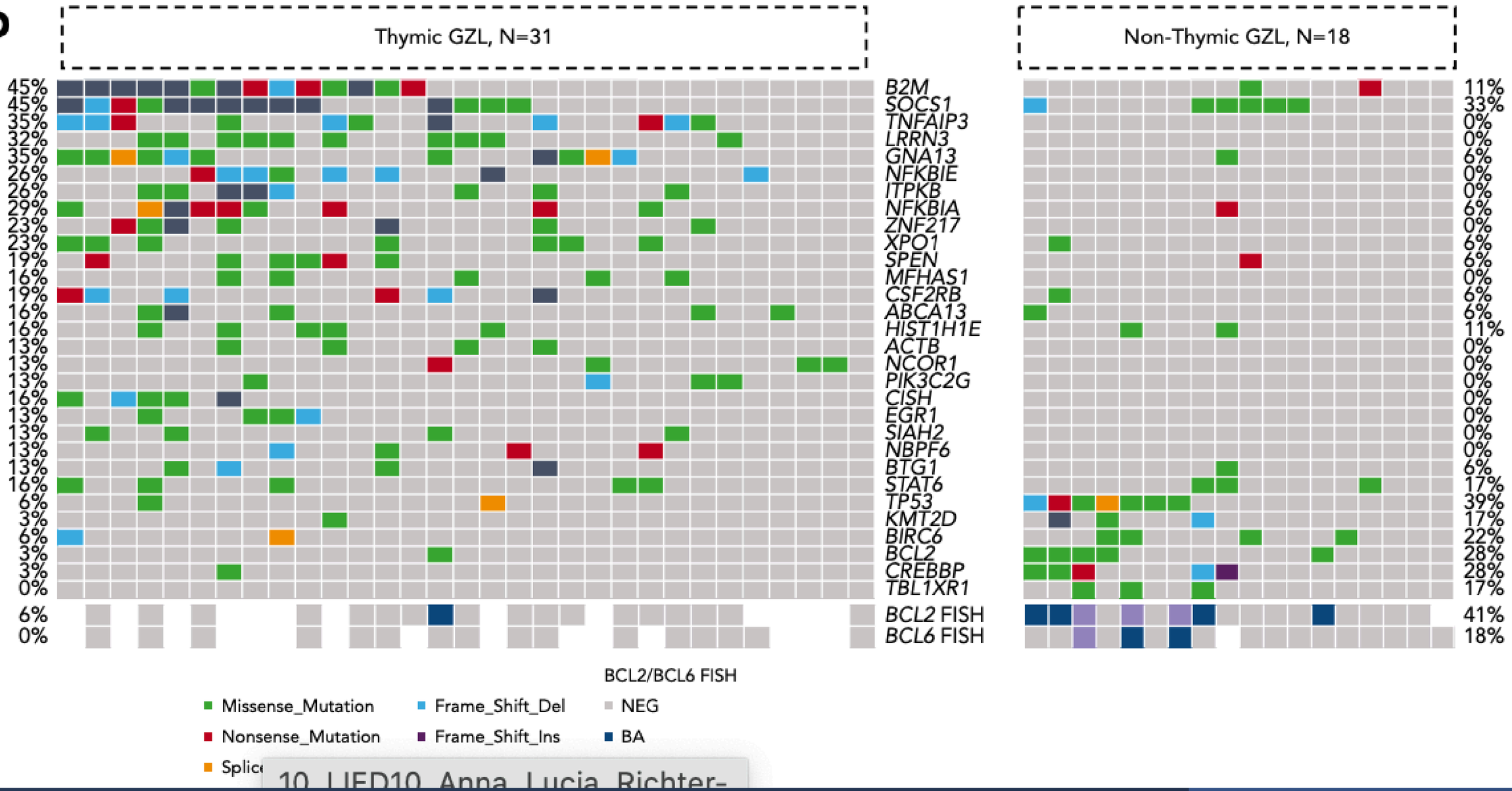
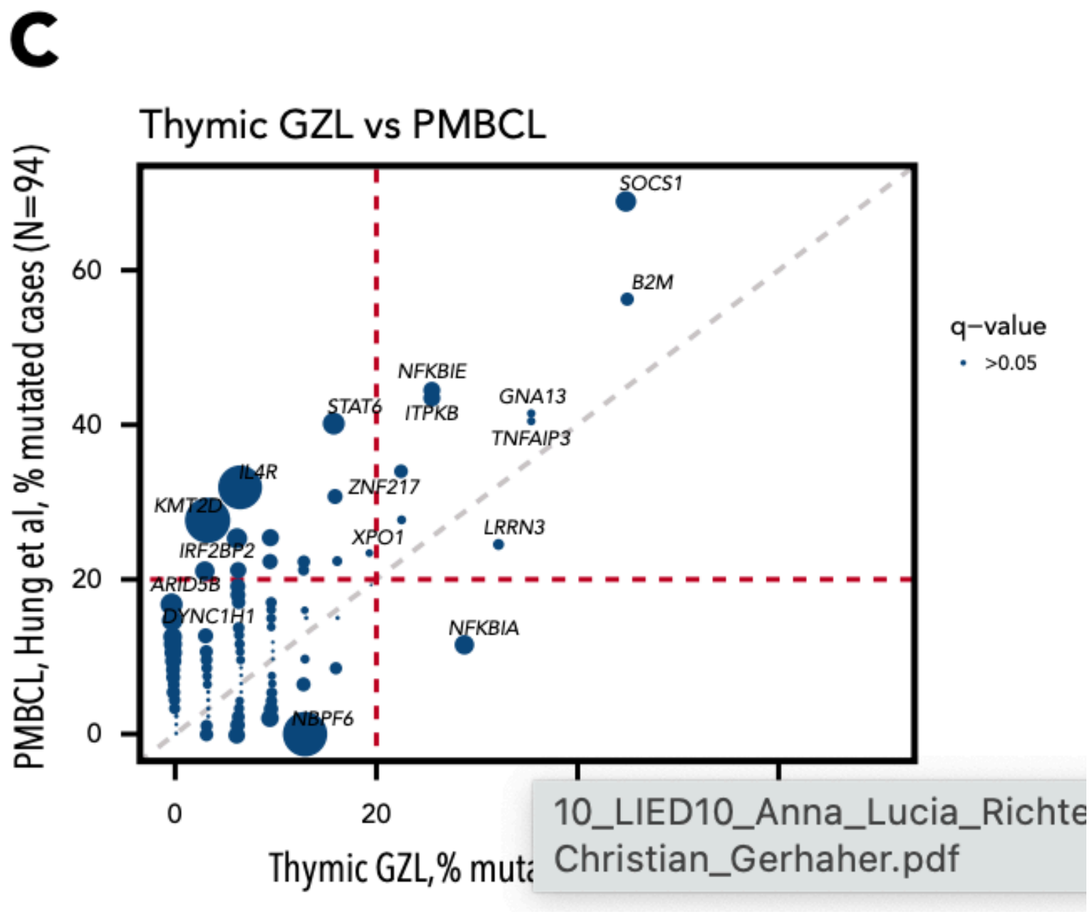

Thymic GZL, N=31
Non-Thymic GZL, N=18
45% B2M 11%
45% SOCS1 33%
35% TNFAIP3 0%
32% LRRN3 0%
35% GNA13 6%
26% NFKBIE 0%
26% ITPKB 0%
29% NFKBIA 6%
23% ZNF217 0%
23% XPO1 6%
19% SPEN 6%
16% MFHAS1 0%
19% CSF2RB 6%
16% ABCA13 6%
16% HIST1H1E 11%
13% ACTB 0%
13% NCOR1 0%
13% PIK3C2G 0%
16% CISH 0%
13% EGR1 0%
13% SIAH2 0%
13% NBPF6 0%
13% BTG1 6%
16% STAT6 17%
6% TP53 39%
3% KMT2D 17%
6% BIRC6 22%
3% BCL2 28%
3% CREBBP 28%
0% TBL1XR1 17%
6% BCL2 FISH 41%
0% BCL6 FISH 18%
BCL2/BCL6 FISH
Missense_Mutation
Frame_Shift_Del
NEG
Nonsense_Mutation
Frame_Shift_Ins
BA
Splic

Comparison with cHL, PMBCL, and DLBCL mutation landscapes

To further understand the distinctions between thymic and nonthymic GZL, we analyzed correlations with the related entities of PMBCL[22] and cHL[23,24] (Figure 4A). As shown in Figure 4B and C, the pattern of mutations observed in thymic GZL was very similar to cHL and PMBCL, without any significant differences after FDR testing for the most recurrently mutated genes (≥20% within each cohort). However, a few distinctions were noted: the incidence of *NFKBIA* mutations (non-sense/frameshift) within thymic GZL (29%) was higher compared with cHL (2.5%; $P = .003$) and PMBCL (12%; $P = .04$), and *NBPF6* mutations were found in 13% of GZL cases (MutSigCV gene; $P = .0008$) but were not reported in cHL or PMBCL. On the other hand, mutations in *IL4R*, a gene recurrently mutated in PMBCL,[37] but not in cHL, were significantly lower in thymic GZL (4%) vs PMBCL (32%; $P = .0007$).



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The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee

A major topic of discussion related to the criteria for **mediastinal gray zone lymphoma** (MGZL). This is the preferred term over what was previously designated B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and CHL. A diagnosis of MGZL requires both morphological (high tumor cell density) and immunophenotypic criteria (at least 2 B-cell markers with strong expression).[203,204] Cases of otherwise typical nodular sclerosis CHL, with variable expression of CD20 are still designated as CHL, although a close biological relationship to primary mediastinal large B-cell lymphoma remains.[205] Sequential primary mediastinal large B-cell lymphoma and nodular sclerosis CHL reinforce the concept of MGZL, as such cases have been demonstrated to be of common clonal origin. However, clinical and genomic data indicate that most non-mediastinal GZL are distinct from MGZL and as such these cases should be diagnosed as DLBCL, NOS. Finally, nearly all EBV-positive DLBCL, while they may contain admixed Hodgkin/Reed-Sternberg-like cells, differ at the genomic level from MGZL, and should be retained within the category of EBV-positive DLBCL.[152,206]

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LYMPHOMA

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

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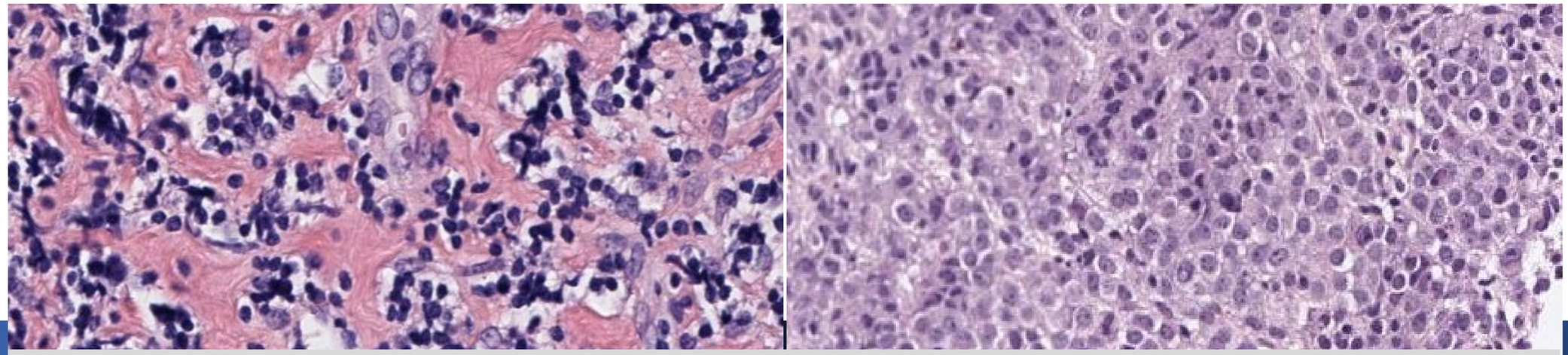
Mediastinal gray zone lymphoma (MGZL) is a B-cell lymphoma with overlapping features between primary mediastinal B-cell lymphoma (PMBL) and classic Hodgkin lymphoma (CHL), especially nodular sclerosis CHL (NSCHL). This entity replaces the term "B-cell-lymphoma, unclassifiable with features intermediate between DLBCL and classic Hodgkin lymphoma" of the WHO-HAEM4R, taking into account that lymphomas with these features are specific to the mediastinum and are part of a single biologic group with a morphologic and immunophenotypic spectrum from CHL to PMBL, with MGZL straddling the two. Current evidence indicates that cases with morphologic and immunophenotypic features similar to MGZL, but occurring outside and without involvement of the mediastinum, harbour different gene expression profiles and DNA alterations [143]. Hence, these cases are better classified as DLBCL, NOS.

Primary Mediastinal LBCL - Clinical

- 2-4% NHL
- Young patients (35 yrs)
- Female > Male
- Bulky mediastinal mass in the thymic region
- Pleural or pericardial effusion is present in one third of cases
- At progression, dissemination to distant extranodal sites, such as the kidneys, adrenal glands, liver, and CNS, is relatively common; however, bone marrow involvement is usually absent
- 5-year survival: 64%

Primary Mediastinal LBCL - Histology

- Large B-cells with interstitial fibrosis, clear cytoplasm, occasional multinucleate pleomorphic cells (HRS-like)
- B-cell markers : CD20, CD79a, PAX5 (>95%)
- Negative for SIg (IHC in paraffin)
- Positive for CD30, CD23, MAL1
- Strong expression of PDL1 and PDL2
- MHC-Class I and II loss



Adaptado de Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375–2390

Primary Mediastinal LBCL - Molecular

- Gains/amplifications in a region of chromosome 9p24.1 including JAK2, PDL1/L2 and SMARCA2
- REL amplification, STAT6 mut, SOCS1 mut.
- Activation of JAK/STAT and NF-kB pathways
- Rearrangements or mutations in the class II-MHC transactivator CIITA at 16p13.13: 53% of PMBLs
- MHC-I loss, B2M mutations

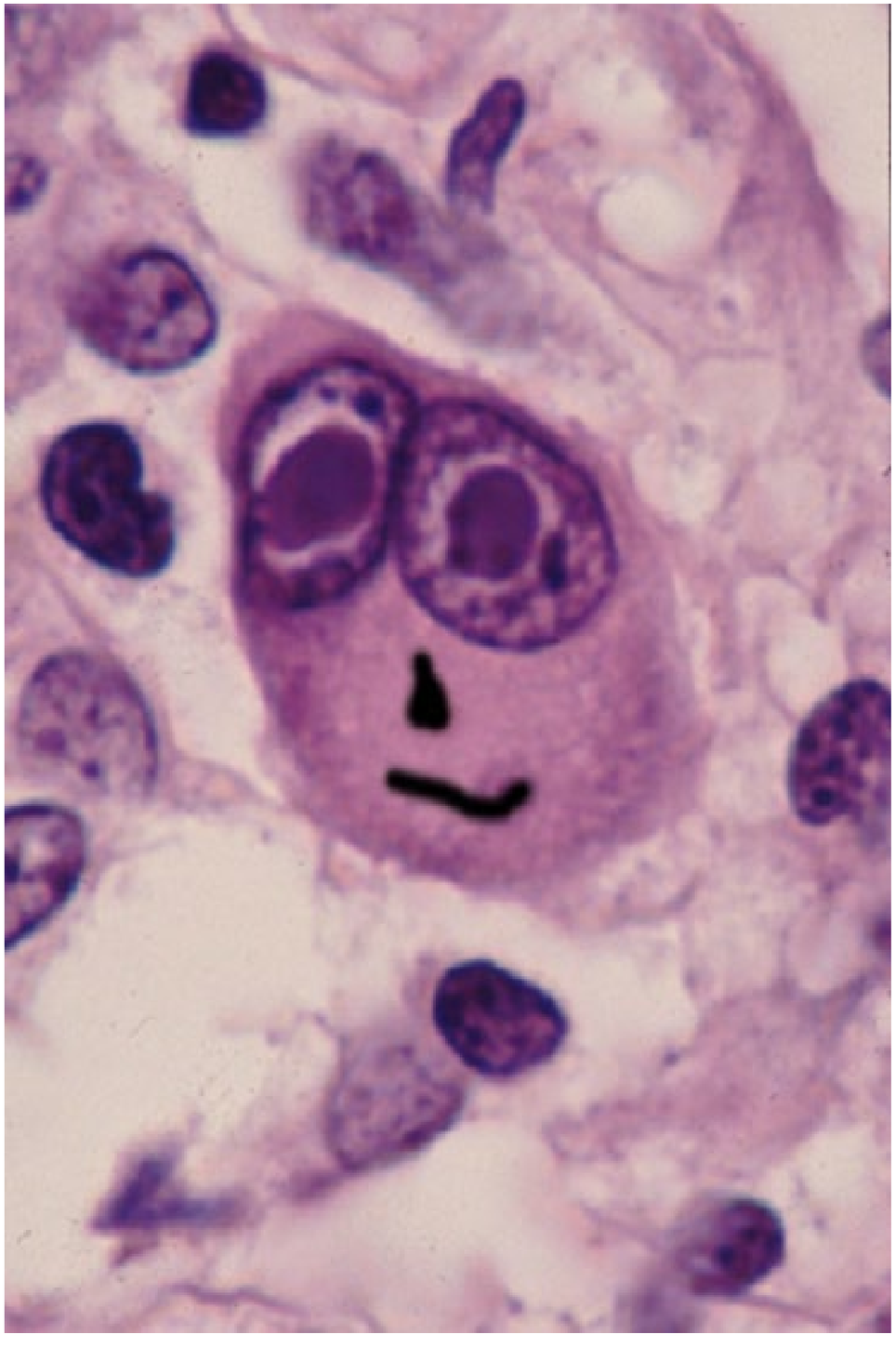
ICC Changes to Hodgkin Lymphoma

- 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. 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 cases, “Fan patterns” A, B and C or Grade 1, be distinguished from “Fan patterns” D, E and F or Grade 2 Cases falling within Grade 2 generally show loss of a well-formed nodular pattern, and increased infiltration by T-cells with reduction of background small B-cells.
- Cases with Grade 2 histology may warrant treatment as DLBCL, but clinical features should play a role in treatment decisions.

ICC Changes to Hodgkin Lymphoma

- The major subtypes of CHL remain unchanged.
- A standard immunohistochemical panel employing CD30, CD15, IRF4/MUM1, PAX5, CD20, CD3 and LMP1 or EBER in situ hybridization is advised.
- Additional immunohistochemical or clonality studies may be warranted in the setting of atypical histological or clinical features.
- A major topic of discussion related to the criteria for mediastinal gray zone lymphoma (MGZL). This is the preferred term.
- A diagnosis of MGZL requires both morphological (high tumor cell density) and immunophenotypic criteria (at least 2 B-cell markers with strong expression).
- Cases of otherwise typical nodular sclerosis CHL, with variable expression of CD20 are still designated as CHL, although a close biological relationship to primary mediastinal large B-cell lymphoma remains.
- Sequential primary mediastinal large B-cell lymphoma and nodular sclerosis CHL reinforce the concept of MGZL, as such cases have been demonstrated to be of common clonal origin.
- Clinical and genomic data indicate that most non-mediastinal GZL are distinct from MGZL and as such these cases should be diagnosed as DLBCL, NOS.
- Nearly all EBV-positive DLBCL, while they may contain admixed Hodgkin/Reed-Sternberg-like cells, differ at the genomic level from MGZL, and should be retained within the category of EBV-positive DLBCL.

Thanks



Change is inevitable, except from vending machines

Woody Allen