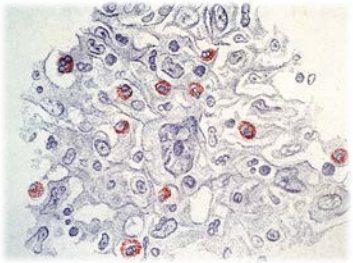
# Hodgkin Lymphoma



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Stanford, California, USA

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## Outline

- Classic Hodgkin Lymphoma (CHL)
- Nodular Lymphocyte Predominant Hodgkin Lymphoma [AKA: Nodular Lymphocyte Predominant B-Cell Lymphoma]
- Differential diagnostic considerations

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## A different kind of disease…

ON SOME
MORBID APPEARANCES
OF
THE ABSORBENT GLANDS
AND
SPLEEN.

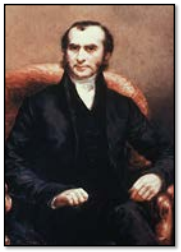
BY DR. HODGKIN.

PRESENTED
BY DR. R. LEE.

READ JANUARY 10TH AND 24TH, 1832.

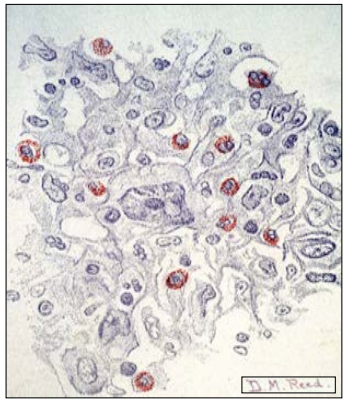
The morbid alterations of structure which I am about to describe are probably familiar to many practical morbid anatomists, since they can scarcely have failed to have fallen under their observation in the course of cadaveric inspection. They have not, as far as I am aware, been made the subject of special attention, on which account I am induced to bring forward a few cases in which they have occurred to myself, trusting that I shall at least escape severe or general censure, even though a sentence or two should be produced from some existing work, couched in such concise but expressive language, as to render needless the longer details with which I shall trespass on the time of my hearers.

- Characteristic clinical presentation
- Contiguous spread
- Inflammation? Infection? Cancer?
- Microenvironment!



**Thomas Hodgkin**
1832

**Dorothy Reed**
1902

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## Classic Hodgkin Lymphoma

Classic Hodgkin lymphoma (CHL) is a neoplasm derived from germinal center B-cells, characterized by a low fraction of tumor cells embedded in a reactive microenvironment rich in immune cells. The large neoplastic Hodgkin and Reed-Sternberg cells show a defective B-cell expression program.

***Subtypes***

- Nodular sclerosis CHL
- Lymphocyte-rich CHL
- Mixed-cellularity CHL
- Lymphocyte depleted CHL

- Basic description and subtypes unchanged
- Vastly increased knowledge of pathogenesis
- Refined criteria excludes mimics: MGZL, NLPHL, THRLBCL, T-cell lymphomas, EBV+ lymphoproliferative disorders
- Recognition of underlying biology, etiology, and epidemiology leading to improved therapeutic options with less toxicity

*WHO HAEM5*

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# CHL: Pathogenesis

### *Genomic Alterations in the Hodgkin cell*

- Aneuploidy and hypertetraploidy
- Recurrent chromosomal imbalances
  - Gains of 2p13 (*REL*), 9p24.1 [CD274 (*PDL1*), PDCD1LG2 (*PDL2*), *JAK2*], 17q21 (MAP3K14)
  - Loss of 6q23-q24 (*TNFAIP3*)
- Recurrent somatic mutations
  - NF-kB pathway (*TNFAIP3, NFKBIA, NFKBIA, REL*),
  - JAK/STAT pathway (*SOCS1, PTPN1, STAT6, STAT3, CSF2RB*)
- Inactivating mutations in immune escape mechanisms
  - MHC class 1 (*B2M*) and MHC class 2 transactivator (*CIITA*)

### Tumor Microenvironment

- Cellular interactions in the CHL TME supports HRS cell survival and/or proliferation by secreting cytokines and chemokines to attract other immune cells

### Immune Evasion

- HRS cells attract T-regs and macrophages and directly suppress cytotoxic CD8+ T-cells and NK-cells by expressing inhibitory surface receptors and secreting immune-suppressive factors

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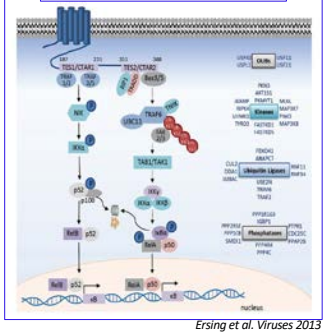
# CHL and EBV

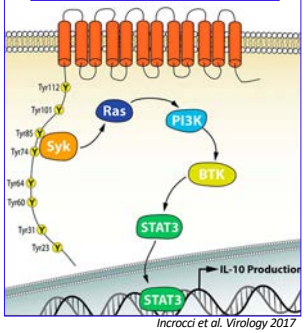
### LMP1 mimics CD40



*Ersing et al. Viruses 2013*

- A subset of CHL harbor EBV
- Latency type II infection
- Express EBERs, EBNA1, LMP1, and LMP2A genes
- LMP1 and LMP2A replace two of the main survival signals of germinal center B-cells

### LMP2A mimics BCR




*Incrocci et al. Virology 2017*

*Kilger et al. EMBO J 1998; Mancao et al. Blood 2007; Kapatai et al. J Clin Pathol 2007*

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## CHL: Clinical Features

- Young adults (~25-35y)
- Epidemiology related to subtypes/ethnicity/socioeconomic factors
- Paraneoplastic features and abnormal lab findings
  - e.g. autoimmune hemolysis, anemia, elevated CRP
- Typically involves LN above the diaphragm: **1RY below diaphragm RARE!**
  - > 70% cervical/supraclavicular; > 60% mediastinal; < 5% infra-diaphragmatic LN or spleen
- Extranodal disease in stage IV disease: **1RY extranodal presentation RARE!**
  - Lung (21%), bone (15%), liver (10%), BM (9%)
  - Atypical sites: Skin, GI tract, mucosal sites, Waldeyer's ring, CNS (additional workup: EBV, HIV, IDD settings)

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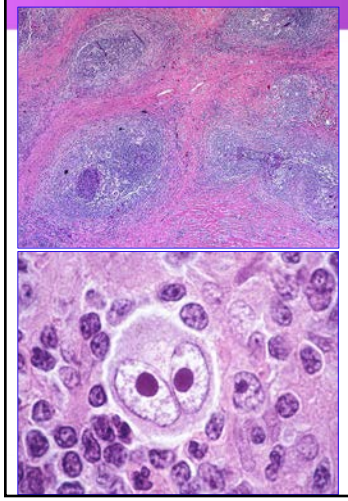
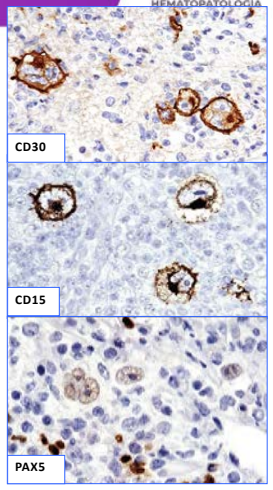
## CHL: Histology & IHC



Highly unusual phenotype for a B cell-derived lymphoma

| Immunophenotype |
|---|
| CD45- Surface Ig- |
| CD20-/+ CD79a- |
| Dim PAX5, OCT2, BOB1 |
| CD30+ |
| CD15+/- |
| MUM1+ |
| EBV+ subset |
| CD3- CD5- CD56- ALK- |
| Newer IHC: PDL1+, STAT6+, GATA3+, MEF2B- |

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## CHL: Treatment and Prognosis

### Current Treatment Strategies

- 80% cured with polychemotherapy +/- radiotherapy
- Treatment tailored to defined risk groups based on staging and to reduce toxicity
- Relapsed/refractory disease
  - Salvage polychemotherapy followed by high dose chemotherapy, auto HSCT, immune checkpoint inhibitors, brentuximab vedotin

### On-going Clinical Trials

**US Intergroup trial (ASCO 2023)**

- Frontline Stage 3-4 disease
  - Nivolumab-AVD superior to BV-AVD for PFS
  - No difference in OS

**Targeting the microenvironment**

- Relapsed/refractory disease
  - CD30 CAR-T trial
  - CD47 (Magrolimab)-Pembro trial
- **Unlike solid tumors, CHL universally expresses PDL1 and levels do not correlate with treatment response**
  - Staining with PD1/PDL1 is not required

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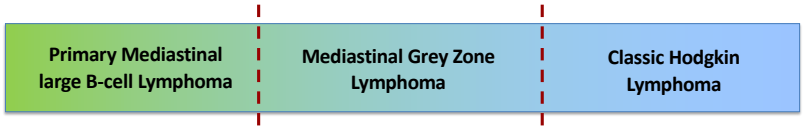
## CHL: Differential Diagnosis




- Mediastinal gray zone lymphoma
- EBV+ lymphoproliferative disorders
- T-cell lymphoma with Hodgkin-like cells
- Lymphocyte-rich CHL with NLPHL and THRLBCL

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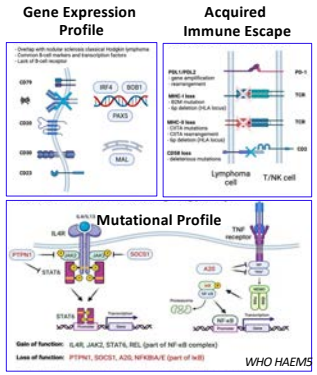
## Primary Mediastinal Large B-Cell Lymphoma

- Aggressive B-cell lymphoma of thymic origin
- Mediastinum in young adults (F>M 2:1)
- Distinct clinical, IHC, and molecular features
- Typically stage I or II
- Favorable prognosis: 85-90% with immuno-chemotherapy
- R/R patients: CAR-T, checkpoint blockade, brentuximab

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## PMBL: Diagnosis

***Essential***

- Large B cell lymphoma in the anterior mediastinum
- Mature B-cell phenotype, accompanied by at least partial expression of CD23 and CD30

***Desirable***

- Distinctive stromal sclerosis
- Expression of at least one of the following markers: MAL, CD200, PD-L1 and PD-L2
- Copy gain or rearrangement of *CD274*/*PDCD1LG2* locus and/or rearrangement involving *CIITA (C2TA)*

*WHO HAEM5*

***Diagnostic Molecular Pathology***

- Not required for routine diagnosis
- Mutation profile may help distinguish PMBL from DLBCL NOS
- GEP can identify PMBL with high accuracy (85%)
- Rearrangements of *CIITA (C2TA),* and aberrant *9p24.1* locus (*JAK2/ PDCD1LG2/CD274*) recurrently found
- *MYC, BCL2, BCL6* rearrangements are rare to absent

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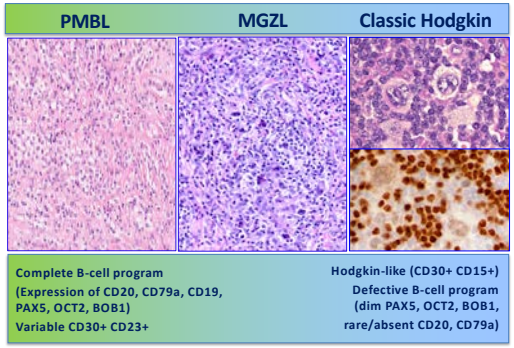
## Mediastinal Grey Zone Lymphoma




- True biological continuum
- Localized, bulky anterior mediastinal mass
- Often with B symptoms; high serum LDH
- Young patients (median 30y), male predominance
- Dissemination below diaphragm and extranodal sites uncommon
- **Defining feature is a mismatch between morphology and immunophenotype**
- Metachronous/sequential cases with shared clonal origin suggest plasticity among entities

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## MGZL: Recommendations for Diagnosis

- Diagnosis of exclusion with a broad morphologic spectrum
- DDX: CHL, PMBL, EBV+ DLBCL, and unusual immunophenotypes
- Needle core biopsies may be insufficient
- Particular pitfalls
  - Marked pleomorphism and HRS-like cells
  - EBV+ MGZL is extremely rare; consider alternative: EBV+ DLBCL, EBV+ LPD
  - "Composite" lymphomas with areas of PMBL and NSCHL within a single tumor
  - Metachronous/sequential lymphomas with PMBL, MGZL or CHL diagnoses over time
- **Multidisciplinary approach recommended**

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## MGZL: Outside the Mediastinum

- Rarely GZL presents outside the mediastinum (primary extranodal (M)GZL or PEMGZL)
- Most are genetically similar to DLBCL, NOS
- GEP: MGZL resembles PMBL; PEMGZL resembles DLBCL, NOS
- PEMGZL has frequent alterations of *TP53, BCL2, BIRC6, CREBBP* with *BCL2* (41%) and *BCL6* (18%) rearrangements, like DLBCL NOS
- Acquired immune escape: *9p24.1* gain/amplification, like PMZL and CHL
- Recommend diagnosis as DLBCL, NOS if disseminated disease with LN, spleen, liver and/or BM involvement is present, esp in older patients

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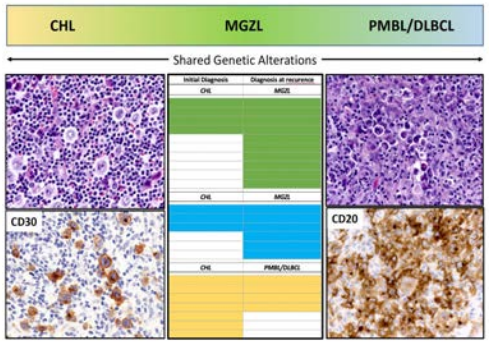
## Mediastinal: Metachronous/Sequential




**Initial diagnosis:** Classic Hodgkin lymphoma
**Recurrence:** Diffuse Large B-cell lymphoma

- Six patients with discordance at relapse
- Targeted mutational profiling showed clonal relationships despite discordant histology
- Most frequent variants included *TNFAIP3* (4/6), *STAT6* (3/5) *ARID1A* (3/6) and *XPO1* (3/5)
- Same oncogenic variant *XPO1* gene (E571K) in 3 of 5, and mutations in *TNFAIP3* and *B2M* observed in 2 of 5 with shared variants
- Metachronous occurrence of CHL shows phenotypic and genetic support for a biological continuum with large B-cell lymphomas
- Mutational profiling could be considered in R/R patients

*Singh et al. AJSP 2023*

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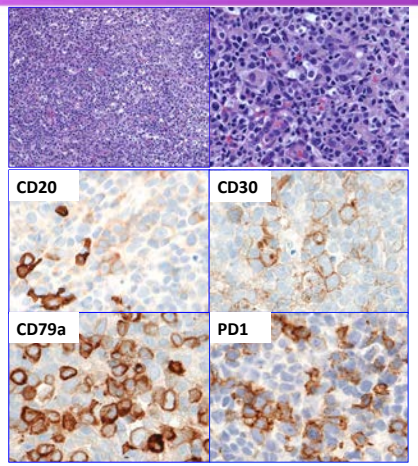
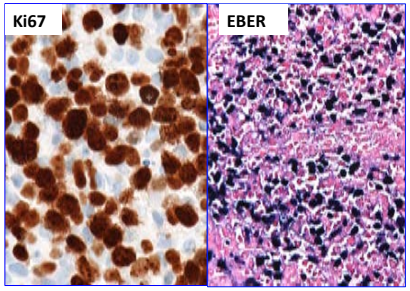
## EBV+ DLBCL

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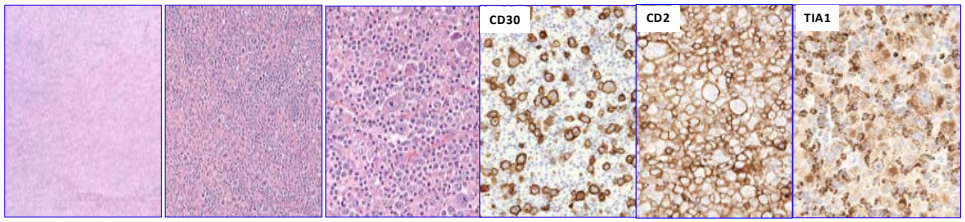
## Peripheral T-Cell Lymphoma with Hodgkin-Like Cells

- 83-year-old woman with supraclavicular, chest, and abdominal lymphadenopathy




- IHC: Negative for CD20, CD79a, PAX5, EBER
- Flow cytometry: Atypical T-cells with CD30 and CD2 expression and loss of CD3, CD5, CD7
- Lacked $T_{FH}$ markers and expanded FDC/CD21
- *TR* rearrangement: Positive
- *IG* rearrangement: Negative

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## NLPHL: Definition

A germinal center-derived B-cell neoplasm composed of scattered large neoplastic B cells with multilobated nuclei (LP cells) within nodules dominated by mantle zone B cells and follicular dendritic cells (FDCs). Variant histological growth patterns also occur in which small B cells are few and/or nodules are infrequent.

***Subtypes (six variant patterns)***

- A: Classic B-cell-rich nodular
- B: Serpiginous/interconnected
- C: Prominent extranodular LP cells
- D: T-cell-rich nodular
- E: Diffuse THRLBCL-like
- F: Diffuse moth-eaten, B-cell-rich

- Basic description and patterns unchanged
- Increased knowledge of pathogenesis
- Refined criteria excludes mimics: LRCHL, THRLBCL, TFL/TCL, PTGC
- Naming and grading differences between WHO/ICC

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## NLPHL: Clinical Features

- Rare type (5%) of Hodgkin lymphoma (0.11 per 100,000 person-years)
- Broad age range: childhood to elderly (30 - 50 years, M:F = 3:1)
- 60% adults and 80% children present with stage I – II disease
- Typically involves peripheral lymph nodes without B symptoms
- 10-year overall survival > 90%; progression-free survival >75%
- Risk of relapse high (unlike classic Hodgkin lymphoma)
- Risk of progression to large B-cell lymphoma, 7-17%
  - Variant immunoarchitectural patterns
  - Splenic and infra-diaphragmatic involvement

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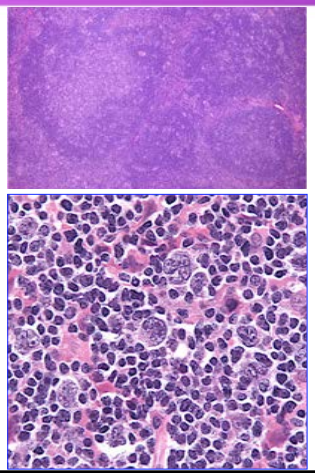
## NLPHL: Histology & Immunophenotype



| Category | IHC Marker | Expression |
|---|---|---|
| **Pan B-cell** | **CD20**, CD79a, CD19 | Positive (rare neg) |
| **B-cell transcription** | PAX5, **OCT2**, BOB1 | Positive |
| **Immunoglobulins** | Kappa/Lambda<br>J-chain<br>IgD | Positive<br>Positive<br>Positive subset |
| **Pan-leukocyte** | CD45RB/LCA | Positive |
| **Pan T-cell** | **CD3**, CD5 | Negative |
| **GC B-cell** | BCL6, HGAL, LMO2, **MEF2B**<br>CD10 | Positive<br>Negative |
| **CHL markers** | **CD30, CD15**<br>STAT6 | Infrequent<br>Negative nuclear |
| **FDC meshworks** | **CD21**, CD23 | Positive |
| **T follicular helper** | **PD1**, ICOS, CD57 | Positive |
| **Immune checkpoint** | PDL1 | Positive |
| **EBV** | **EBER** | Rare |
| **Other** | MUM1/IRF4<br>EMA<br>IgG4 | Positive<br>Positive<br>Negative |

*Younes et al. Cancers 2021*

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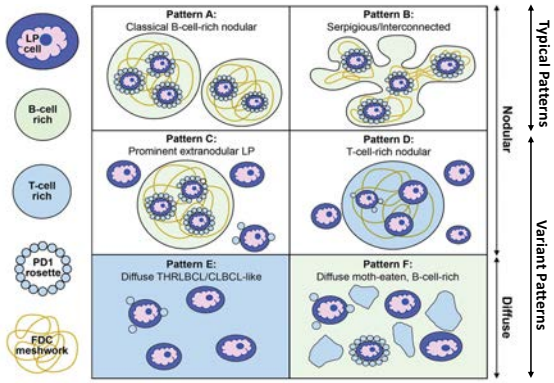
## NLPHL: Six Patterns




*Fan et al, Am J Surg Pathol 2003*
*Younes et al. Cancers 2021*

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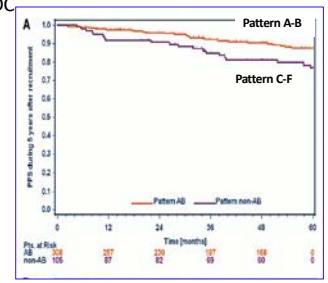
## Clinical Impact of Variant Patterns

- **Stanford study**
  - Extranodular LP cells: propensity for diffuse pattern and loss of FDC
  - Pattern E (TCRBCL-like): independent predictor of recurrence
- **German Hodgkin Study Group**
  - Typical (75%: A, B) and variant (25%: C, D, E, F) patterns
  - Variant patterns: independent prognostic factor a/w advanced clinical stage and higher relapse rates
- **Pediatric age group**
  - Variant patterns a/w higher stage & relapse rates, lower CR

- Insufficient data on individual versus mixed patterns (%)
- Insufficient data for grading: grade 1 (A-C) vs grade 2 (E-F)




*Fan et al. Am J Surg Pathol 2003*
*Hartmann et al. Blood 2013*
*Shankar at al. Br J Haematol 2015*
*Binkley et al. Blood 2020*
*Campo et al. Blood 2022*

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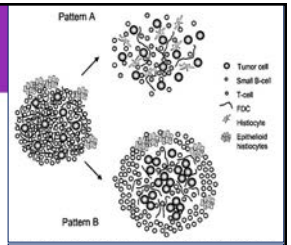
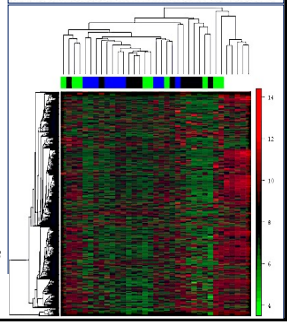
## NLPHL-THRLBCL/DLBCL Continuum

- Transformation of NLPHL occurs in 7-17%
- Pattern E/THRLBCL-like areas overlap with THRLBCL
  - Architecture, LP cell distribution and frequency, TME composition, GEP signatures, and mutation profiles
- Individual cases may show wide variation
- A true biologic continuum is increasingly recognized but large validation studies are needed

**NLPHL** — **Variant E/THRLBCL-like** — **THRLBCL/DLBCL**



*Boudova et al. Blood 2003*
*Hartmann et al. PloS One 2013*

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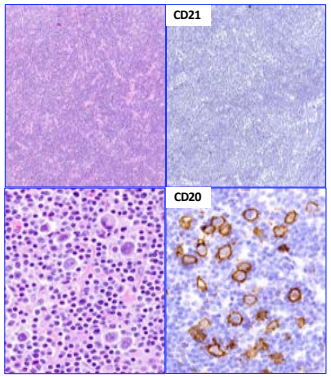
## T-Cell/Histiocyte-Rich Large B-Cell Lymphoma

- Diffuse architecture with limited large B cells
- Abundant TFH type T-cells and histiocytes in TME
- Arises de novo or transforms from NLPHL
- Middle-aged men
- B symptoms, splenomegaly, hepatomegaly common
- >50% advanced stage
- Aggressive clinical course; variable in tNLPHL
- IPI correlated with prognosis; no other robust markers
- Staging essential to distinguish from vNLPHL

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## NLPHL: Genetic Landscape

- LP cells harbor recurrent genetic alterations and deregulated signaling pathways
  - NLPHL: *SGK1, DUSP2, JUNB*
  - THRLBCL: *SGK1, DUSP2, JUNB, SOCS1, CREBBP*
- Transformed NLPHL has distinctive profiles
  - Comparable # genomic alterations to de novo DLBCL
  - Frequent mutations in PI3K and NF-kB pathways and epigenetic modifiers (similar to GCB DLBCL)
  - Frequent mutations in *TET2, JUNB, NOTCH2* (uncommon in DLBCL)
  - tNLPHL resembles tFL, likely due to the loss of TME during transformation

| Pathway/Type of Alteration | Mutated in tNLPHL |
|---|---|
| PI3K pathway | SGK1, ZFP36L1 |
| NF-kB pathway | CARD11, JUNB, BCL10, TNFAIP3 |
| JAK/STAT pathway | SOCS1 |
| Epigenetic modifiers | EZH2, KMT2D |
| CN gains | REL (56%), BCL11A, BCL6, CARD11, JAK2 |
| CN loss | CDKN2A |
| Uncommon in de novo DLBCL | JUNB (21%), TET2 (11%), NOTCH2 |
| Immune surveillance (BM2, MHC I-II, CD58) TP53 | Uncommon in tNLPHL |

*Al-Mansour et al. J Clin Onc 2010*
*Hartmann et al. Leukemia 2016*
*Reddy et al. Cell 2017*
*Schuhmacher et al. Haematologica 2018*

***Song et al. Leukemia 2020***
*Chapuy et al. Nat Med 2018*
*Schmitz et al. NEJM 2018*
*Wright et al. Cancer Cell 2020*
*Lacy et al. Blood 2020*

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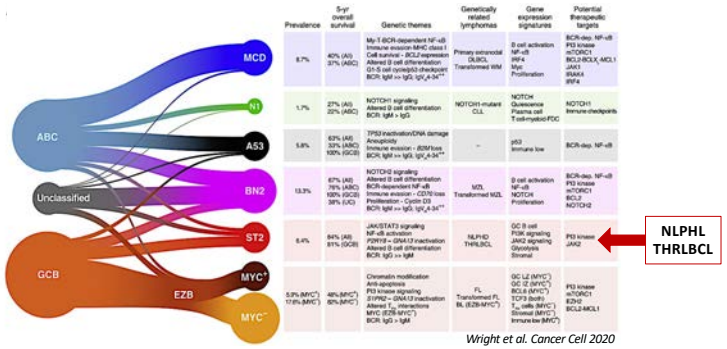
## Correlation with Genetic Subtypes of DLBCL

- Genetic subtypes show similarity with indolent lymphomas indicative of shared pathogenesis
- Gene expression profiling suggest activation of innate immune response in NLPHL




*Wright et al. Cancer Cell 2020*

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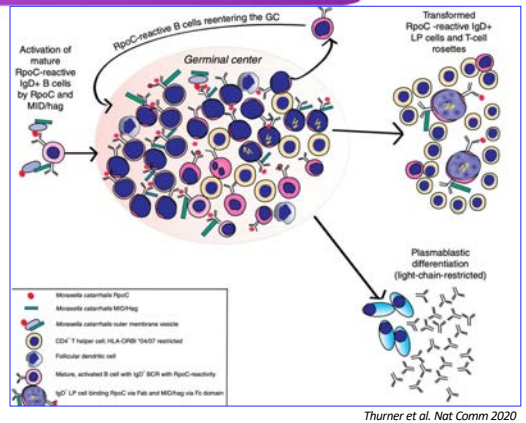
## NLPHL: Bacteria as Trigger for Lymphomagenesis

- Detection of RNA polymerase (RpoC) of ***Moraxella catarrhalis*** as frequent antigen of BCRs of IgD+ LP cells
- *Moraxella*-induced activation triggers B-cell receptor signaling, NF-κB activation and IgD+ LP cell proliferation
- **Pathogen-induced antigen stimulation of B-cells as a model of NLPHL lymphomagenesis**




*Thurner et al. Nat Comm 2020*

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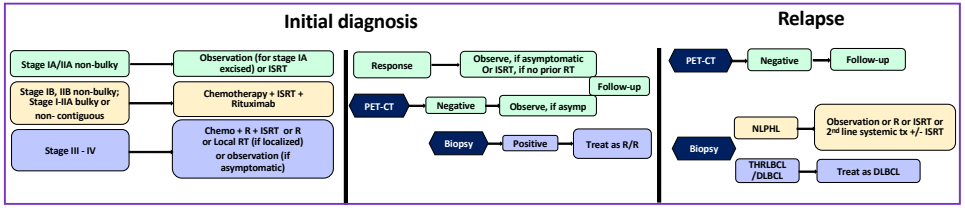
## NLPHL: Prognosis and Prediction

- No standardized therapy: observation, rituximab, radiotherapy, chemotherapy or combinations

- **Adult patients:** ILROG study stage 1 – II: OS 98%, PFS 87%, Transformation 3.8%
- Variants patterns: consider alkylator (CHOP-based) therapy

- **Pediatric patients**: 5y OS 100%, EFS 85%, >75% spared chemo, >90% spared RT
- Intermediate risk patients treated like CHL (ABVE-PC + IFRT)
- Variant patterns: higher stage, lower CR, more relapses; no change in therapy




*Drs. Ranjana Advani, Richard Hoppe & Michael Binkley, Stanford*
*Binkley et al. Blood 2020: ILROG Study*
*NCCN Guidelines*

*Dr. Michael Link, Stanford Children's Hospital; Donaldson et al. J Clin Onc 2007: VAMP*
*Metzger et al. JAMA 2012: VAMP; Appel et al. J Clin Oncol 2016: COG Study*
*Marks et al. Ped Blood Cancer 2018: COG Study; Shankar et al. Euro J Cancer 2012: Br J Haematol 2015*

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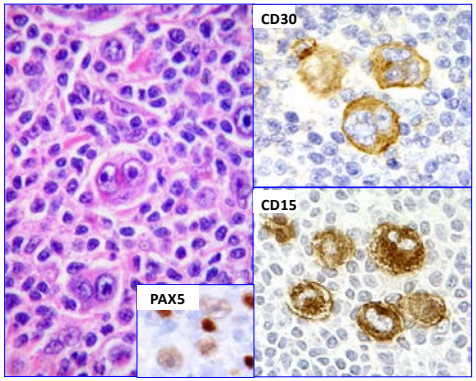
## Lymphocyte-Rich Classic Hodgkin Lymphoma

- Nodular or less commonly diffuse infiltrate of small lymphocytes with an absence of eosinophils and neutrophils
- CD30+ CD15+ HRS cells
- May have regressed GCs within nodules
- Small IgM+ IgD+ mantle zone lymphocytes within nodules
- Significant overlap of NLPHL with LRCHL (1 of 3 in older datasets)
- Additional IHC markers helpful to distinguish CHL from NLPHL
  - CD79a, MEF2B, CD19
  - PDL1, STAT6, GATA3

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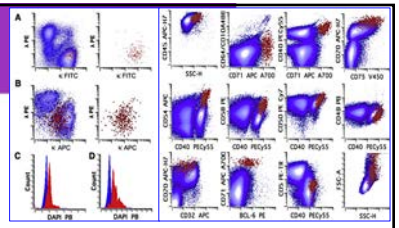
## Unusual Phenotypes

- **NLPHL with increased T-cells may mimic a T-cell lymphoma**
  - No pan-T antigen loss
  - Frequent CD4+/CD8dim+ T-cell population
  - Variable immunophenotypes (TH, TFH, TREG…)
  - Absence of *TR* gene rearrangements
  - Similarity in clinical behavior to THRLBCL?
- **NLPHL with EBV**
  - EBV+ in LP cells or bystander small B-cells
  - More likely to be CD30+ CD15- PAX5/CD79 variable
  - Type II latency similar to CHL
  - Is EBV primary vs transient driver?



*Fromm et al. Am J Pathol 2017; Sohani et al. Am J Surg Pathol 2011; Ohgami et al, AJCP 2014; Treetipsatit et al. Hum Pathol 2015*

| | All Patients (n = 302) | EBV$^+$ (n = 12) | EBV$^-$ (n = 290) |
|---|---|---|---|
| Age, median | 19 (4-80) | 25.5 (4-62) | 19 (4-80) |
| M:F ratio | 5.2:1 | 5:1 | 5.3:1 |
| CD20 | 99% (299/301) | 100% (12/12) | 99% (287/289) |
| CD79a | 98% (49/50) | 100% (6/6) | 98% (43/44) |
| PAX5 | 100% (73/73) | 100% (8/8) | 100% (65/65) |
| OCT-2 | 99% (166/167) | 100% (11/11) | 99% (155/156) |
| BOB.1 | 90% (43/48) | 60% (3/5) | 93% (40/43) |
| BCL6 | 96% (117/122) | 91% (10/11) | 96% (107/111) |
| EMA | 42% (59/142) | 0% (0/8) | 44% (59/134) |
| CD30 | 28% (75/270) | 75% (9/12) | 25% (66/258) |
| CD15 | 3% (8/266) | 0% (0/12) | 3% (8/254) |
| IgD | 57% (119/208) | 20% (2/10) | 59% (117/198) |

*Huppmann et al. Am J Surg Pathol 2014; Wang et al. Ann Diag Pathol 2014 Gerhard-Hartmann et al. Histopathology 2022; Fei et al. Am J Clin Pathol 2022*

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## Summary & Future Directions

- Definitions and boundaries surrounding CHL and NLPHL reflect increased knowledge of the pathogenesis
- True biologic continuum becoming increasingly recognized
- Advances in understanding the genetic landscape and microenvironment drive improvements in targeted therapy with less toxicity
- Robust and reproducible criteria needed to better define risk groups
- Large validation studies to better understand the clinical impact of rare variants
- A multidisciplinary approach improves patient care (*free resource!*)

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