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# Nodular lymphocyte-predominant Hodgkin lymphoma

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ABSTRACT

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare subtype of Hodgkin lymphoma with distinct clinicopathologic features. It is typified by the presence of lymphocyte predominant (LP) cells, which are $CD20^+$ but $CD15^-$ and $CD30^-$ and are found scattered amongst small B lymphocytes arranged in a nodular pattern. Despite frequent and often late or multiple relapses, the prognosis of NLPHL is very favorable. There is an inherent risk of secondary aggressive non-Hodgkin lymphoma (NHL) and studies support that risk is highest in those with splenic involvement at presentation. Given disease rarity, the optimal management is unclear and opinions differ as to whether treatment paradigms should be similar to or differ from those for classical Hodgkin lymphoma (CHL). This review provides an overview of the existing literature describing pathological subtypes, outcome and treatment approaches for NLPHL


## 1. Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare subtype of Hodgkin lymphoma (HL), accounting for ~5% of all HLs. Patients with NLPHL typically present with asymptomatic early-stage disease with peripheral lymph node involvement. Unlike classical Hodgkin lymphoma (cHL), late and often multiple relapses have been widely reported [1] but despite this, the prognosis is generally favorable with deaths due to NLPHL extremely uncommon.

Due to disease rarity, information on the natural history of NLPHL and appropriate management is mostly ascertained from retrospective series or the evaluation of subsets enrolled in larger randomized controlled HL trials with very few prospective studies. After 1993, EORTC-GELA (European Organization for Research and Treatment of Cancer–Groupe d'Etude des Lympomes de l'Adulte) study groups excluded NLPHL from larger HL clinical trials and a separate clinical registry was created. In contrast, NLPHL patients have typically been included as part of the GHSG (German Hodgkin Study Group) trials.

## 2. Pathology of NLPHL

NLPHL is characterized by a nodular or nodular and diffuse growth pattern with scattered large neoplastic cells originally referred to as lymphocytic and/or histiocytic Reed-Sternberg cell variants (L&H cells). In the updated 2008 World Health Organization (WHO) classification the malignant cells were renamed as lymphocyte predominant (LP) cells and, due to the characteristic multi-lobated or folded appearance of the nucleus, they are often referred to the descriptive term "popcorn" cells [2].

Surrounding the tumor cells are $CD4^+$ T lymphocytes that show typically a follicular helper T-cell phenotype with co-expression of CD57 and PD1 [3,4], supporting derivation of this lymphoma from the germinal center (GC). Furthermore, cases with cytomorphologic atypical T cells, mimicking peripheral T-cell lymphoma (PTCL)-not otherwise specified (NOS), have been described that behave clinically similar to T-cell–rich B-cell lymphoma (TCRBCL)-like NLPHL [5]. The importance of pathologic review of older cases was highlighted from the European Task Force Study where only 56% of submitted cases of presumed NLPHL were confirmed by today's diagnostic standards [6].

In contrast to the Hodgkin and Reed-Sternberg (HRS) cells in cHL that express CD15 and CD30, LP cells are usually negative for these antigens and retain instead expression of B-cell markers, including CD20 and CD79a as well as CD45 and epithelial membrane antigen (EMA) [2] (see Table 1). Moreover, LP cells usually express the B-cell transcription factors OCT-2 and BOB.1 [7] and are positive for BCL6 and activation-induced cytidine deaminase (AID), further emphasizing the GC origin, although CD10 is largely negative [8]. However, despite the fact that most of the classical B-cell markers maintain expression, it has been shown that several B-cell genes (eg, CD19, CD37, LCK) are downregulated in LP cells contributing to a partial loss of the B-cell phenotype [9,10]. Epstein-Barr virus (EBV) is typically negative Table 2.

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**Table 1**
Histologic and immunophenotypic comparison of NLPHL, cHL, and TCRBCL.

| | NLPHL | cHL | TCRBCL |
|---|---|---|---|
| **Malignant cells** | LP cells | HRS cells | Scattered large B cells |
| **Morphology** | Nodular, nodular and diffuse | Diffuse, interfollicular, nodular | Diffuse, vaguely nodular |
| **Reactive background** | Mostly small B cells, $CD4^+CD57^+PD1^+$ T cell rosettes | Lymphocytes, histiocytes, eosinophils, plasma cells T-cells > B-cells | Mostly small $CD8^+$ T cells, $CD68^+$ histiocytes |
| **Immunophenotype** | $CD20^+$, $CD21^+$, $CD79a^+$, $CD75^+$, $BCL6^+$, $EMA^{+/-}$[a], J $chain^{+/-}$ $slg^{+/-}$ $CD15^-$ CD30-[b] | $CD20^{-/+}$, $CD21^{+/-}$ (varies by subtype), $CD45^-$ $CD79a^{-/+}$[b], $EMA^-$ J $chain^-$ $CD15^{+/-}$ $CD30^+$ | $CD20^+$, $CD21^-$ $CD45^+$, $CD79a^+$, $CD75^+$, $BCL6^+$, $EMA^{+/-}$ J $chain^{+/-}$ $slg^{+/-}$, $CD15^-$ CD30-[b] |
| **Transcription factors** | $PU.1^{+/-}$ $PAX5^+$, $OCT\text{-}2^+$, $BOB.1^+$ | $PU.1^-$ $PAX5^+$ [c], $OCT\text{-}2^{-/+}$, $BOB.1^-$ | $PU.1^{-/+}$, $PAX5^+$, $OCT\text{-}2^+$, $BOB.1^+$ |
| **EBER** | Absent [d] | Varies depending on subtype, about 50% | Rare |

+ = all cases positive; +/- = majority of cases positive; -/+ = minority of cases positive; - = all cases negative;
NLPHL = nodular lymphocyte-predominant Hodgkin lymphoma; cHL = classical Hodgkin lymphoma; TCRBCL=T-cell–rich B-cell lymphoma.

[a] EMA-positive in 50%.
[b] Positive in rare cases.
[c] Up to 10% may be negative.
[d] EBER rarely expressed in NLPHL and does not preclude the diagnosis.

A more detailed characterization of histopathological variants of NLPHL has been provided by Fan et al [11] who described six immunoarchitectural growth patterns (Figure 1). Typical histologic growth patterns include classic nodular B-cell–rich (pattern A) and serpiginous/interconnected nodular (pattern B) types, both of which demonstrate a predominantly nodular growth with non-neoplastic B cells and LP cells located within the nodules (Fig. 1). In contrast, the so-called histopathologic variants have LP cells outside the nodules and/or reduced B cells within the nodules, and include the following four patterns: nodular with predominance of extranodular LP cells (pattern C), nodular T-cell–rich (pattern D), diffuse TCRBCL-like (pattern E), and diffuse (B-cell–rich) moth-eaten (pattern F) (Fig. 1). Of importance, a mixture of patterns was more often seen than pure patterns and about 8% of cases did not have a classical nodular pattern, highlighting the importance of recognizing variant growth patterns for rendering the diagnosis of NLPHL.

Although the number of cases with available clinical data was limited in this initial study, it was noted that a diffuse TCRBCL-like pattern was associated with a higher rate of recurrent disease. More recently, the GHSG evaluated the prognostic significance of these histological variants in over 400 NLPHL patients and demonstrated that the histological variant group (patterns C–E above) was associated with a higher stage at presentation (29.5% *v* 14.6%) and a higher relapse rate [12].

## 3.2. Molecular signature of NLPHL

### *3.1. Dysregulation of signaling pathways*

A common feature of cHL and NLPHL is frequent aberrant activation of the JAK-STAT signaling pathway, in part due to inactivating mutations of the negative regulator SOCS1 [13,14], which in LP cells results in nuclear accumulation of pSTAT6. Gene expression–based studies further revealed strong overlap with cHL with an upregulation of nuclear factor-κB (NF-κB) target genes [9]; however, unlike in cHL, mutations in *NFKBIA* and *TNFAIP3*, encoding for the NF-κB pathway inhibitors IκBα and A20, respectively, rarely occurs in NLPHL [15].

**Table 2**
Comparison of clinical features of NLPHL, cHL and TCRBCL.

| | NLPHL (GHSG, n = 394) | cHL (GHSG, n = 7,904) | TCRBCL (n =6 1) |
|---|---|---|---|
| **Median age (y)** | 37 | 33 | 30 |
| **Male sex (%)** | 75 | 56 | 71 |
| **Stage III-IV (%)** | 21 | 39 | 65 |
| **B symptoms (%)** | 9 | 40 | 46 |
| **Mediastinal involvement (%)**[a] | 31 | 55 | 32 |
| **Extranodal (%)** | 6 | 14 | 61 |
| **≥3 nodal areas** | 28 | 55 | – |

NLPHL = nodular lymphocyte predominant Hodgkin lymphoma; cHL = classical Hodgkin lymphoma; TCRBCL = T-cell–rich B-cell lymphoma

[a] Mediastinal involvement in ETFL study was only 7% [1].

### *3.2. Genomic alterations*

The most common structural genomic alteration described in NLPHL is translocations of *BCL6*, occurring in about 50% of cases and either involving the *Ig* heavy chain locus or other genes [16]. The paucity of tumor cells in conjunction with the rarity of NLPHL has largely precluded a comprehensive exploration of the mutational landscape in this disease. Hartmann et al recently reported on whole-genome sequencing of the diffuse large B-cell lymphoma (DLBCL) component of two composite NLPHL/DLBCL cases and subsequent targeted re-sequencing of 62 genes on whole-tissue sections from 16 cases of an extension cohort [17]. Novel recurrent mutations in *DUSP2*, *SGK1,* and *JUNB* (each of these genes mutated in about 50% of cases) were identified, in addition to mutations affecting known oncogenes or tumor-suppressor genes such as, *TP53*, *BRAF*, *PTPN1*, *ATM*, *BCOR,* and *EP300*. Since the mutations were seemingly enriched in the transformed lymphomas or in NLPHLs presenting with a variant histopathological growth pattern, it remains unclear to what extent these alterations truly reflect the biology of classical NLPHL or if they rather represent genomic aberrations associated with a more aggressive disease behavior.

## 4. Relationship to other pathological entities

### *4.1. Progressive transformation of germinal centers*

Progressive transformation of germinal centers (PTGC) is a benign condition characterized by enlarged follicular structures with expanded mantle zones, the latter often intruding into the GC. Although large centroblasts as well as higher numbers of $CD4^+CD57^+$ and $CD4^+CD8^+$ T cells can be found, PTGCs lack typical LP cells and T-cell rosettes [18]. PTGC can occur prior to, concurrent with, or after the diagnosis of NLPHL in patients [19,20].

### *4.2. NLPHL and TCRBCL*

The distinction between TCRBCL-like NLPHL (Fan pattern E) and TCRBCL is difficult because there is considerable diagnostic