



Review Article



Histopathologic Features and Differential Diagnosis in Challenging Cases of Nodular Lymphocyte Predominant B-cell Lymphoma/Nodular Lymphocyte Predominant Hodgkin Lymphoma

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Abstract

Nodular lymphocyte predominant Hodgkin lymphoma was termed “nodular lymphocyte predominant B-cell lymphoma” in the International Consensus Classification (ICC), to emphasize clinical and biological differences from classic Hodgkin lymphoma (CHL). The abbreviation “NLP” represents both terms in the ICC and World Health Organization classifications. Variations in the growth pattern, originally reported as Fan patterns A–F, are designated as either grade 1 or grade 2 in the ICC. NLP is uncommon, and in some cases an accurate diagnosis is challenging. The objectives of this article were to review the histopathologic features of NLP and the differential diagnosis from other key entities including de novo T-cell/histiocyte-rich large B-cell lymphoma (THRLBL) and lymphocyte-rich classic Hodgkin lymphoma (LRCHL). Histologically, NLP Fan pattern E (THRLBL-like) can be indistinguishable from de novo THRLBL. However, focal nodular areas, clustering of tumor cells, presence of few admixed small B-cells or FDC meshworks, and T-cell rosettes favor NLP Fan pattern E and argue against de novo THRLBL. NLP may also be confused with LRCHL. Patients with NLP are younger than those with LRCHL, and LRCHL may show mediastinal involvement. In LRCHL, the nodular pattern often contains eccentrically located small regressed germinal centers and intact small dense FDC meshworks, in contrast to the expanded, and fragmented FDC meshworks in NLP. Neoplastic cells that are positive for CD30 and CD15 but negative for CD20 and CD79a are characteristic of LRCHL. Additionally, Fascin and Gata3 are commonly positive in LRCHL but usually negative in NLP.

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Introduction

Nodular lymphocyte predominant Hodgkin lymphoma, alternatively termed nodular lymphocyte predominant B-cell lymphoma in the International Consensus Classification (ICC), is uncommon. Some cases can present challenges in diagnosis and may be difficult to differentiate from other entities with similar histologic features.^{1,2} The objectives of this article were to review the histopathologic features of this disease, abbreviated as NLP, and to provide some clues in its differentiation from de novo T-cell/histiocyte-rich large B-cell lymphoma (THRLBL) and lymphocyte-rich classic Hodgkin lymphoma (LRCHL).

History and terminology

Early on, NLP was identified as a B-cell neoplasm and later shown to be of germinal center derivation.^{3,4} It is characterized by either nodular or nodular and diffuse proliferation, containing scattered large mononucleated or multilobated neoplastic cells known as lymphocyte-predominant (LP) cells or popcorn cells.^{5,6} This entity was previously categorized as one of the variants of Hodgkin lymphoma, most likely due to the histologic features, including sparse neoplastic cells and abundant non-neoplastic cells in the background, similar to classic Hodgkin lymphoma (CHL). A proposal from the International Lymphoma Study Group first suggested a more formal separation of NLP from CHL in 1994.⁷ Subsequently, based on data indicating greater differences in clinical behavior and treatment approaches, the ICC took this a step further by recommending the removal of the eponymic term “Hodgkin”, from the disease, proposing the term “nodular lymphocyte predominant B-cell lymphoma” to emphasize emerging differences in clinical management for these two lymphomas of B-cell lineage.⁸ Currently, the term “nodular lymphocyte predominant Hodgkin lymphoma” remains unchanged in the 5th Edition of the World Health Organization classification. In the following discussion, NLP will be the abbreviation for both nodular lymphocyte predominant Hodg-

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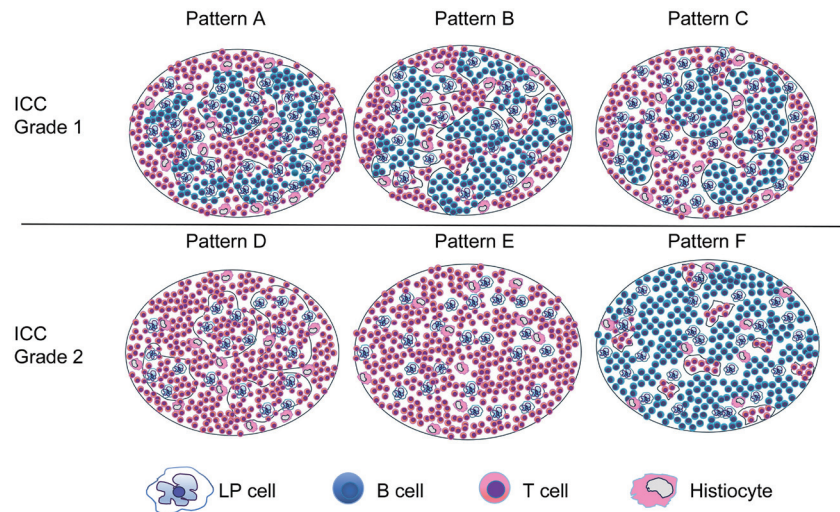


Fig. 1. Schematic diagram of histopathologic patterns in NLP and relevant ICC grades. Fan pattern A, so-called classical B-cell-rich nodular pattern: Clusters of single LP cells are embedded within enlarged follicles/nodules predominantly composed of small B-cells. Reactive T-cells are mainly in the interfollicular areas. The FDC meshworks are expanded and associated with the atypical follicles/nodules. Fan pattern B, so-called serpiginous/interconnected pattern: Similar to Fan pattern A, LP cells are mainly within B-cells rich atypical follicles/nodules, which interconnect with each other. Fan pattern C, so-called prominent extra-nodular LP cells pattern: LP cells extend beyond the follicular compartment with an internodular distribution. Fan pattern D, so-called T-cell-rich nodular pattern: LP cells distribute in a vaguely nodular pattern, but normal follicular B-cells are lost, and the atypical nodules are rich in T-cells. FDC meshworks are usually still present. Fan pattern E, so-called diffuse pattern (THRLBL or DLBCL-like): The growth pattern is diffuse. LP cells are widely scattered in a background rich in T-cells and histiocytes. FDC meshworks are lost and normal admixed B-cells are largely absent. Fan Pattern F, the so-called diffuse moth-eaten, B-cell-rich pattern: The LP cells are scattered in a background that is rich in both small B-cells and T-cells. The FDC meshworks are absent. Per ICC classification, Fan Patterns A, B, and C are categorized as grade 1, and Fan patterns D, E, and F are categorized as grade 2. DLBCL, diffuse large B-cell lymphoma; FDC, follicular dendritic cells; NLP, nodular lymphocyte predominant Hodgkin lymphoma/nodular lymphocyte predominant B-cell lymphoma; ICC, International Consensus Classification; LP, lymphocyte-predominant; THRLBL, T-cell/histiocytes-rich large B-cell lymphoma.

kin lymphoma and nodular lymphocyte predominant B-cell lymphoma.

Epidemiology and clinical features

NLP is more common in young patients (aged 30–50 years) with a male predominance and comprises 10% of all Hodgkin lymphomas.⁹ Patients usually present with localized lymphadenopathy initially, most commonly involving cervical, axillary, and inguinal lymph nodes or rarely mesenteric lymph nodes. Mediastinal and extranodal involvements are uncommon. Overall, the disease demonstrates an indolent clinical course and an excellent outcome with standard therapy.^{10,11} Systemic B symptoms are uncommon in the absence of advanced disease. Approximately 20% of patients can present with advanced-stage disease at diagnosis with involvement of the spleen, liver, or more rarely bone marrow and bone.¹² Transformation of NLP into diffuse large B-cell lymphoma occurs in 5–10% of cases.^{11,13}

Epstein-Barr virus (EBV) has been thought to play a significant role in the pathogenesis of some CHL subtypes. However, it is only rarely positive in NLP (< 5%).^{14,15} LP cells can be positive for IgD in a subgroup of patients, particularly young male patients with isolated neck or axillary lymphadenopathy.^{16–18} A subset of IgD+ cases were found to be associated with *Moraxella catarrhalis* and *Rothia mucilaginosa* in recent studies,^{19,20} suggesting a potential role for bacterial antigens in the stimulation of the B-cells that ultimately give rise to the LP cells of NLP.

Microscopy

NLP has a nodular growth pattern in most cases and a diffuse pattern in fewer cases (Figs. 1 and 2a). The initial lesion

appears to arise within pre-existing reactive follicles. The follicular structures are usually larger than normal follicles and are associated with expanded follicular dendritic cell (FDC) meshworks. LP cells show a rim of pale cytoplasm, large twisted or multilobated nuclei with thin nuclear membranes, vesicular chromatin, and basophilic nucleoli, which are usually smaller than those in Hodgkin/Reed-Sternberg (HRS) cells (Fig. 2a). Multilobated LP cells have been likened to a “popped kernel of corn”, termed “popcorn cells”. Multinucleated cells may be observed. LP cells reside in an immune niche in a background of predominantly small lymphocytes with a variable number of histiocytes. Occasionally, significantly increased histiocytes, clusters of epithelioid histiocytes, or granulomas can be appreciated.

Various growth patterns of LP cells and the associated lymphocytic background were initially described by Fan *et al.* (Fig. 1).²¹ The most common growth patterns in NLP are Fan patterns A and B, comprising about 75% of cases. LP cells are scattered singly but commonly show vague clustering within the follicular structures/nodules of small B-cells with a few reactive T-cells. As the disease progresses, normal small B-cells decrease, while admixed T-cells become more abundant. In addition, Fan pattern C shows LP cells extending beyond the follicular compartment. Further loss of normal B-cells is evident in Fan pattern D. Evidence of follicular remnants disappears in Fan pattern E, which may be entirely diffuse. This THRLBL-like transformation is difficult to differentiate from de novo THRLBL. Fan pattern F also shows loss of follicular structures with a vaguely nodular background containing both B-cells and T-cells, lacking FDC meshworks (Fig. 1).

Immunohistochemical (IHC) stains are crucial to identify the various growth patterns, and more than one pattern can be observed in a single lymph node biopsy. The significance of the various growth patterns was recognized

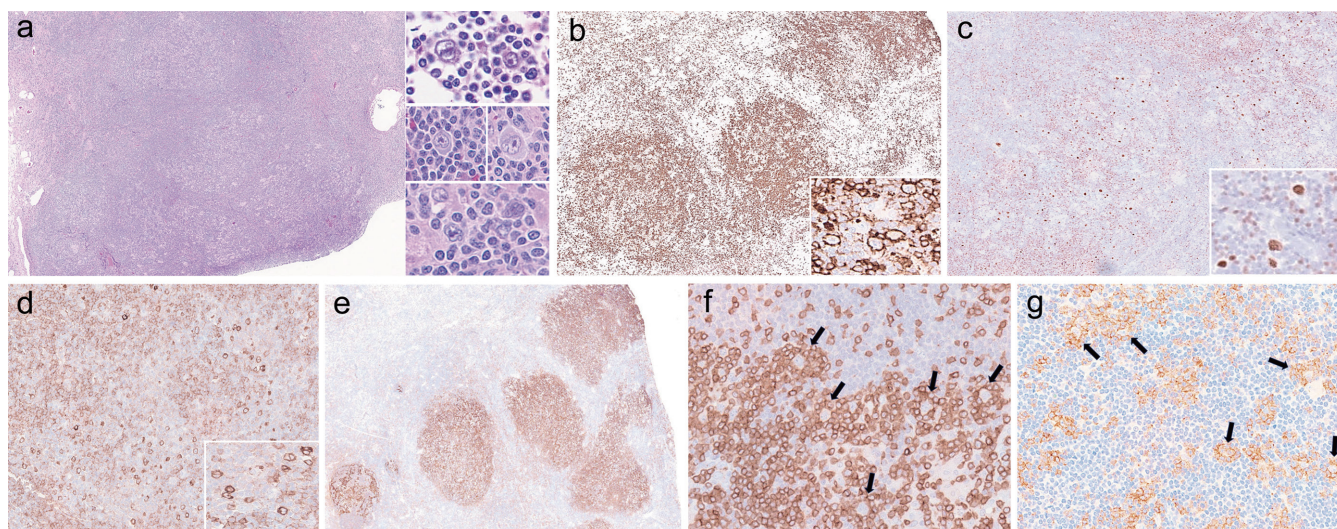


Fig. 2. The histologic and immunohistochemical features of NLP. (a–c) NLP Fan pattern A. (a) H&E stain section shows a vaguely nodular pattern with expanded atypical follicles lacking normal germinal centers. LP cells are largely confined to the follicular remnants (original magnification 4×); the insets show LP cells at high power (original magnification 80×). (b) The abnormal follicles are rich in CD20+ small B-cells (original magnification 4×); the inset shows LP cells at higher power (original magnification 40×). (c) Oct-2 highlights LP cells. Staining is strong in LP cells and weak in background small B-cells (original magnification 10×); the inset shows LP cells at higher power (original magnification 30×). (d) This case of NLP involving the tonsil contains LP cells that are positive for IgD (original magnification 10×); the inset at higher power (original magnification 30×). The background small B-cells are also positive for IgD. (e–g) NLP, Fan pattern A (same case as a–c). (e) CD21 highlights the nodular pattern delineated by the FDC meshworks (original magnification 2×). (f) CD3 and (g) PD-1 highlight T-cell rosettes, which surround the LP cells (arrows) (original magnification 30×). FDC, follicular dendritic cells; H&E, hematoxylin and eosin; LP, lymphocyte-predominant; NLP, nodular lymphocyte predominant Hodgkin lymphoma/nodular lymphocyte predominant B-cell lymphoma; Oct-2, Octamer-binding protein 2; PD-1, programmed cell death protein 1.

in ICC grading, with Fan patterns A, B, and C being grade 1, while Fan patterns D, E, and F considered grade 2.^{8,21} Patients with grade 2 disease may warrant treatment as diffuse large B-cell lymphoma, especially with advanced clinical stage.²²

Reactive follicular hyperplasia, often with foci of progressive transformation of germinal centers (PTGC), may be seen in adjacent uninvolved nodal tissue. PTGC was reported to precede, follow, or occur concurrently with NLP. However, isolated PTGC is not a significant risk for subsequent NLP.^{23,24} The follicular structures in PTGC are markedly enlarged, largely as a consequence of the mantle zone expansion. The resultant follicle contains clusters of germinal center cells surrounded by IgD-positive cells. However, typical LP cells are not present. In addition, PTGC follicles are usually enriched for T follicular helper (TFH) cells stained by programmed cell death protein 1 (PD-1) and CD57. Therefore, an increase in TFH cells should not raise significant concern for involvement by NLP.

Immunophenotype

LP cells typically demonstrate strong expression of transcription factors Octamer-binding protein 2 (Oct-2) and B cell Oct binding protein 1 (Bob1), which are critical for functional immunoglobulin (IG) expression. They also maintain other B-cell associated markers such as CD20, CD79a, paired box protein 5 (Pax5), PU-1, and B-cell lymphoma 6 (Bcl-6) but are usually negative for multiple myeloma 1/interferon regulatory factor 4 (MUM-1/IRF4) and CD10 (Fig. 2b). In our experience, Oct-2 facilitates the detection of the neoplastic cells, especially when there are abundant small background B-cells. The background non-neoplastic B-cells show weak staining for Oct-2, as they are typically derived from the residual mantle cuffs (Fig. 2c). Pax5 is positive, but more weakly expressed in tumor cells than background B-cells. In addition, myocyte enhancer binding factor 2B (MEF2B) is

expressed in LP cells.^{25–27} IgD was reported to be positive in 27% of cases, particularly affecting young male patients (Fig. 2d).^{16–18} LP cells are generally negative for EBV-encoded small RNA (EBER), with EBER rarely positive in 3–5% of cases.^{14,15,28–30} In some cases LP cells show downregulation or absence of some B-cell markers, such as CD20, Pax5, or CD79a,³¹ particularly in EBV+ cases.¹⁴

FDC markers such as CD21 and CD23 highlight the expanded and often fragmented FDC meshworks in the atypical nodules (Fig. 2e). NLP arises in preexistent follicles. Over time, the background normal B-cells disappear and are replaced by infiltrating T-cells. Most of the T-cells associated with the neoplastic LP cells exhibit a TFH phenotype and are strongly positive for PD-1/CD279. They form tight rosettes around the LP cells, which can help facilitate their detection (Fig. 2f–g). Prolonged close contact between LP cells and the surrounding PD-1+ T-cells was observed and may play a role in tumorigenesis.^{32,33} However, rosette formation with PD-1+ T-cells is not specific for NLP; it can be found in CHL but is usually less conspicuous.^{34,35} CD57+ cells are also common in the background of NLP.

Genetic findings

The LP cells possess functional IG rearrangements and express IG transcripts, which are more easily detected in DNA from isolated tumor cells or in tumor-rich samples. However, IG rearrangements are challenging to detect in whole tissue sections with sparse neoplastic cells and rich non-neoplastic cells in the microenvironment. LP cells typically exhibit a high load of somatic hypermutation in IGH variant regions with ongoing mutations, indicating the derivation from germinal center B-cells.⁴ FISH (fluorescence in situ hybridization) analysis may reveal gene rearrangement of *BCL6* with partners including IG genes, *IKAROS* family genes, *ABR*, and others.^{36–38} Next generation sequencing study found mutations in *PAX5*, *PIM1*, *RHOH* (*TTF*), and *MYC*,³⁹ as well as so-

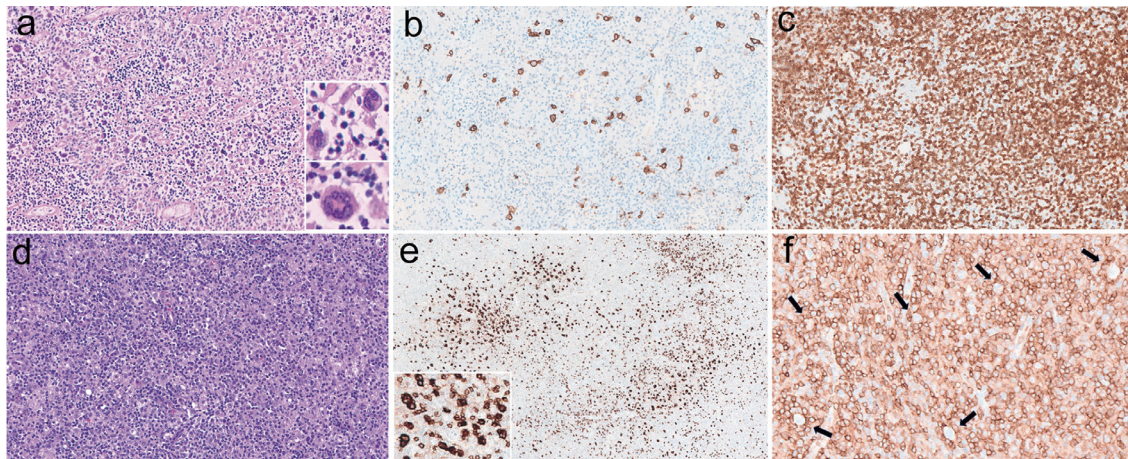


Fig. 3. The histologic and immunohistochemical features of THRLBL vs. NLP Fan pattern E. (a–c) Representative images of THRLBL. (a) H&E stain section of THRLBL involving the spleen (original magnification 20×); the insets show neoplastic cells with pleomorphism (original magnification 80×). (b) CD20 highlights the widely scattered large neoplastic cells with the absence of background small B-cells in a case of THRLBL involving the bone marrow (original magnification 20×). (c) CD3 shows the T-cell-rich background (original magnification 20×). (d–f) Representative images of NLP Fan pattern E involving a lymph node (H&E) (original magnification 20×). (e) LP cells forming loose clusters are highlighted by CD20 (original magnification 4×); the inset shows LP cells at high power; a few small B-cells are present in the background (original magnification 30×). (f) CD4 highlights background T-cells forming rosettes around the LP cells (arrows) (original magnification 30×). H&E, hematoxylin and eosin; LP, lymphocyte-predominant; NLP, nodular lymphocyte predominant Hodgkin lymphoma/nodular lymphocyte predominant B-cell lymphoma; THRLBL, T-cell/histiocytes-rich large B-cell lymphoma.

matic mutations in *SGK1*, *DUSP2*, and *JUNB* in some cases of NLP.⁴⁰ LP cells share mutations in *JUNB*, *DUSP2*, *SGK1*, and *SOC31* with THRLBL which suggests a close relationship between these two entities.⁴¹ Aberrations in *TNFAIP3* or *NFKB1A* are rare in LP cells,⁴² unlike in HRS cells of CHL. Instead, the active *NFκB* signaling gene signature in LP cells results from different mechanisms.^{43–45} Familial NLP has been reported in patients with Hermansky-Pudlak syndrome type 2 and autoimmune lymphoproliferative syndrome with mutations in *FAS*.^{46,47}

Challenging cases of NLP and differential diagnosis

Genetically, the tumor cells of NLP and THRLBL exhibit marked similarity, suggesting they are part of a single entity. The differential diagnosis between LRCHL and NLP can also be challenging in some cases. Herein, we discuss some helpful tips for accurate diagnosis in challenging cases of NLP.

NLP, Fan pattern E vs. THRLBL

NLP Fan pattern E shows sparse tumor cells dispersed in a rich inflammatory background composed largely of T-cells and histiocytes. Background FDC meshworks and nodular areas may be absent or only focally seen. The background T-cells are predominantly CD4+ T-cells, while CD8+ T-cells have been reported to be more frequent in THRLBL (Figs. 1 and 3).

THRLBL is considered an aggressive B-cell lymphoma with sparse large tumor cells scattered in a background of abundant T-cells and/or histiocytes. It most frequently affects middle-aged or older male patients, whereas NLP often affects relatively younger patients, including children. Patients with THRLBL typically present with advanced disease with B symptoms, bulky lymphadenopathy, and/or hepatosplenomegaly. Systemic involvement is much more common than in NLP and frequently involves the spleen, liver, bone marrow, and bone, in addition to lymph nodes.

Tumor cells in THRLBL carry clonal IG gene rearrangement and high levels of somatic mutations. The genomic profile is similar to that of NLP, further supporting a close relationship.^{48,49}

Histologically, tumor cells in THRLBL are evenly dispersed in a background of diffuse T-cells with a variable number of histiocytes. The tumor cells may exhibit variations in size or pleomorphism, and lobated nuclei can be present in some cases (Fig. 3a). A nodular growth pattern is not appreciated on H&E-stained sections. Focal residual nodules, if present, confirm NLP Fan pattern E and argue against de novo THRLBL. Other subtle differences may be helpful. In THRLBL, the background usually contains more histiocytes and fine fibrosis, whereas fibrosis is less often encountered in lymph nodes involved by NLP. Necrosis is also more commonly found in THRLBL.

The immunophenotype of the tumor cells in THRLBL is similar to that of NLP (Fig. 3b). They are negative for CD15, CD30, and EBER in most cases. By flow cytometry, the phenotype of the neoplastic cells in THRLBL and NLP is nearly identical, limiting the utility of flow cytometry for differential diagnosis.^{50,51} Nevertheless, in THRLBL, the background lymphocytes are more often CD8+ T-cells with an absence of small B-cells (Fig. 3b–c).⁵² These T-cells show strong activation by 3D measurement.⁵³ PD-1+ T-cell rosettes surrounding tumor cells are generally absent. FDC meshworks are absent as well. In contrast, LP cells in NLP Fan pattern E may still show vague clusters, best highlighted by CD20 and Oct-2 (Fig. 3d–e). In addition, a few residual scattered small B-cells, traces of FDC meshworks, and T-cell rosettes all favor the diagnosis of NLP Fan pattern E (Fig. 3e–f).

In some cases, a clear distinction between THRLBL and NLP Fan pattern E may not be possible. However, if NLP is observed in another site or at the time of recurrence, the diagnosis of NLP may be confirmed.

Morphologic and IHC features of the two entities are summarized in Table 1.

NLP vs. LRCHL

LRCHL is a subtype of CHL with scattered HRS cells in a background rich in small lymphocytes and usually lacking other inflammatory cells, such as plasma cells and eosinophils. It is less common than NLP and usually affects older patients compared to NLP and other CHL subtypes, showing a male

Table 1. Differential diagnosis of NLP: Summary of histopathologic and IHC features

		THRLBL	NLP	LRCHL
Neoplastic cells	Morphologic features	Sparse, widely dispersed, variable degrees of pleomorphism. May resemble centroblasts or immunoblasts	Sparse, multilobated nuclei, thin nuclear membranes, basophilic nucleoli. Tend to form loose clusters. May be intrafollicular or interfollicular.	Sparse; may resemble lacunar cells or classic HRS cells. Most common in the marginal zone surrounding regressed follicles.
	CD30	–/+	Negative to weakly +	Strongly +
	CD15	–	–/rare +	+/–
	EBER	–	Rarely EBV+	EBV + (15–20%)
	EMA	variable	–/+	–
	Pan-B cell markers	+	+	–/weak and variable +
	MUM-1	–/+	–/+	+, strong
	Oct-2	+, strong	+, strong	–/+
	Pax5	+	+, (may be weak)	+, weak
	Others	N/A	Positive for MEF2B; may be positive for STAT6 in rare cases	Often positive for Fascin, Gata-3, and STAT6
Non-neoplastic Background	Morphologic features	Diffuse lymphocytic background with increased histiocytes and fine fibrosis	Nodular or diffuse lymphocytic background. Variable histiocytes.	Mainly nodular pattern. Regressed follicles present. Rare to absence of eosinophils, neutrophils and plasma cells. Diffuse pattern less common
	CD20	Absence of small B-cells	Background B-cells nearly always present	Intact follicles
	CD4/CD8	Often CD8> CD4	Mainly CD4+	Mainly CD4+
	T-cell (PD-1+) rosettes	Absent	Present	Sometimes seen
	CD21/CD23	Absent	Expanded FDC meshworks	Compact tight intact FDC meshworks

EBER, EBV-encoded small RNA; EBV, Epstein-Barr virus; EMA, epithelial membrane antigen; FDC, follicular dendritic cells; Gata3, GATA-binding protein 3; LRCHL, lymphocyte-rich classic Hodgkin lymphoma; MEF2B, myocyte enhancer binding factor 2B; MUM-1, multiple myeloma 1/interferon regulatory factor 4; NLP, nodular lymphocyte predominant Hodgkin lymphoma/nodular lymphocyte predominant B-cell lymphoma; Oct-2, Octamer-binding protein 2; Pax5, paired box protein 5; PD-1, programmed cell death protein 1; THRLBL, T-cell/histiocytes-rich large B-cell lymphoma.

predominance. Patients with LRCHL show an indolent clinical course, and B symptoms are rare. The disease mainly affects peripheral lymph nodes. Mediastinal involvement is less common than in nodular sclerosis CHL but can be present, while mediastinal disease is rare in NLP. The prognosis of LRCHL is somewhat better than other CHL subtypes.¹²

Histologically, the most common form of LRCHL exhibits a nodular growth pattern (Fig. 4a–f).^{1,54} The follicles contain regressed germinal centers and intact mantle zones. CD21 or CD23 highlights small, dense, compact, and intact FDC meshworks associated with the eccentrically located regressed germinal centers (Fig. 4b). The HRS cells are best observed in the marginal zone, surrounding the regressed follicles. This pattern contrasts with what is seen in NLP, where the LP cells are scattered within the altered follicles (Fig. 4g–i). LRCHL with a diffuse pattern is rare and probably closer to the mixed cellularity subtype of CHL.

The HRS cells in LRCHL may resemble “lacunar” type HRS cells with ample cytoplasm and sometimes multilobated nuclei (Fig. 4a). They can also resemble LP cells. The HRS cells exhibit the typical immunophenotype of CHL with strong staining for CD30, CD15 (subset), MUM-1, and dim expression of Pax5 (Fig. 4c–e). CD20 and CD79a are most

often negative but can be variably expressed. Occasionally, HRS cells in this subtype can express variable B-cell transcription factors such as Oct-2, Bob-1, and Bcl-6. EBER and latent membrane protein 1 (LMP1) can be positive or negative (Fig. 4f). It should be noted that LP cells in NLP can be rarely positive for CD30 or CD15.^{21,55–57} However, if positive, CD30 staining tends to be weak in LP cells (Fig. 4i). EBV-positive NLP is another rare finding (Fig. 4j).^{14,15} In reported cases, Oct-2 usually remains strongly expressed. (Fig. 4k)

Other markers reported in the differential diagnosis of LRCHL and NLP include fascin, GATA-binding protein 3 (Gata-3), and STAT6. These antigens are more likely to be positive in the HRS cells of CHL than in LP cells.^{58–61} The specificity of STAT6 expression in HRS cells is controversial.^{61,62} In addition, HRS cells also show strong staining with MUM-1, generally negative in LP cells. While epithelial membrane antigen has been reported to be positive in LP cells, the incidence of truly positive cases is low. A recent study showed that light chain restriction can be demonstrated by ultrasensitive in situ hybridization for kappa and lambda in LP cells but not in HRS cells.⁶³ PD-1+/CD57+ T-cell rosettes around HRS cells can be present but are usually less common than in NLP

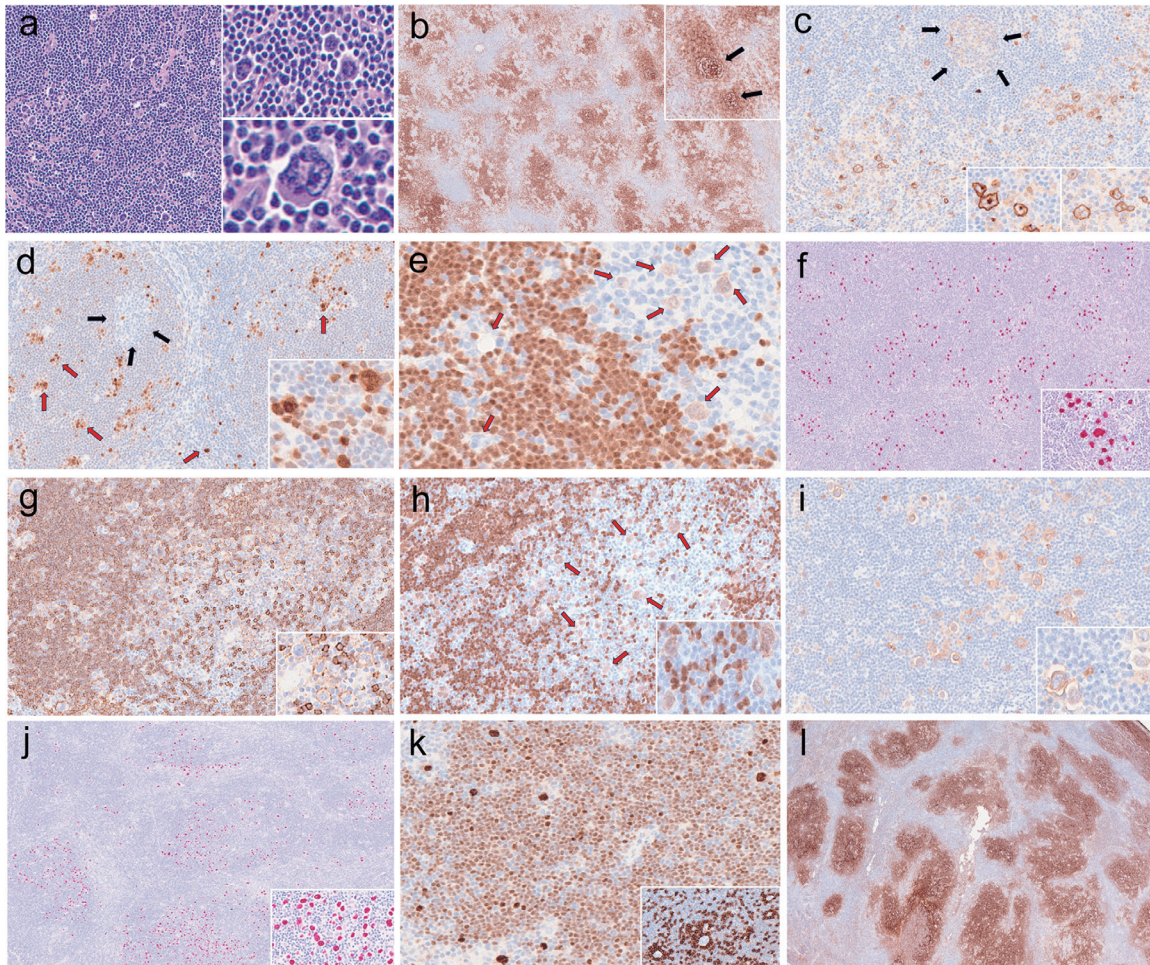


Fig. 4. The histologic and immunohistochemical features of LRCHL vs. EBV+ NLP. (a–f) Representative images of LRCHL, EBV+. (a) H&E stain section of LRCHL involving a lymph node (original magnification 30×); the insets show HRS cells at higher power (original magnification 40× and 80×). (b) CD21 shows the regressed lymphoid follicles and tight FDC meshworks (original magnification 2×); the inset shows eccentrically located compact FDC meshworks (arrows), which are associated with regressed germinal centers (original magnification 20×). (c) CD30 highlights the HRS cells with strong and homogeneous staining mainly in the interfollicular and marginal zone areas; the eccentrically located regressed germinal center is highlighted by arrows (original magnification 15×); the insets show HRS cells at higher power (original magnification 40×). (d) MUM-1 is positive in HRS cells with strong staining (red arrows), outside the small regressed germinal center (black arrows) (original magnification 10×); the inset shows HRS cells at higher power (original magnification 40×). (e) Dim staining for Pax5 in HRS cells (red arrows) (original magnification 40×). (f) HRS cells positive for EBER (original magnification 4×, inset 40×). (g–l): Representative images of EBV+ NLP Fan pattern A. (g) CD20 shows downregulated CD20 expression with variable staining in LP cells (original magnification 10×, inset 40×). (h) Pax5 expression is downregulated in LP cells (red arrows) (original magnification 10×, inset 40×). (i) CD30 highlights clusters of LP cells with weak and variable staining (original magnification 10×, inset 40×). (j) EBER highlights clusters of LP cells (original magnification 4×, inset 40×). (k) Oct-2 highlights LP cells with strong staining, in contrast to weaker staining in background small B-cells (original magnification 20×). The inset (CD3) shows T-cell rosettes around LP cells (original magnification 30×). (l) CD21 shows expanded and fragmented FDC meshworks with irregular contours (original magnification 2×). EBER, EBV-encoded small RNA; EBV, Epstein-Barr virus; FDC, follicular dendritic cells; H&E, hematoxylin and eosin; HRS, Hodgkin/Reed-Sternberg; LP, lymphocyte-predominant; LRCHL, lymphocyte-rich classic Hodgkin lymphoma; MUM-1, multiple myeloma 1/interferon regulatory factor 4; NLP, Nodular lymphocyte predominant Hodgkin lymphoma/nodular lymphocyte predominant B-cell lymphoma; Oct-2, Octamer-binding protein 2; Pax5, paired box protein 5.

(Fig. 3k, inset).

Specific studies focusing on the genomic features of HRS cells in LRCHL have not been published. In other work, the failure of HRS cells to express IG transcripts has been partially attributed to a deficiency in the transcription factors Oct-2 and Bob-1. It is of interest that these transcription factors are more often positive in LRCHL.⁵⁵ Whether this impacts Ig expression in the neoplastic cells is unknown.

The genomic profile of HRS cells differs from that of LP cells in NLP and may provide clues for their distinction if available. HRS cells show alterations in both the NF-kappa B and JAK/STAT pathways.^{64–66} These include mutations of *SOCS1*.^{67–70} The other frequent genetic abnormalities in-

clude gains of 2p, 9p, 16p, 17q, 19q, and 20q, losses of 6q, 11q, and 13q, as well as aberrations of 9p24.1 leading to amplification of *JAK2* and increased expression of PD-1 ligands.^{71,72} Inactivating *B2M* mutations, as well as driver mutations in *BCL7A*, *GNA13*, and *PTPN1*, are also detected in CHL.^{73,74}

Morphologic and IHC features of the two entities are summarized in Table 1.

Conclusions

NLP is an uncommon form of lymphoma. In recent years, there has been a greater appreciation of its distinctive clinical

and biological features, with emphasis on major differences from CHL. This information has led to changes in the clinical management of NLP. For these reasons, an accurate diagnosis is of major importance to the practicing pathologist. The lymph node biopsy should always be examined with knowledge of the clinical history. Key diagnostic features include the nature of the neoplastic cells, as well as the characteristic microenvironment. In addition, ancillary techniques, including immunohistochemistry, can lead to the correct interpretation in most cases.

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Conflict of interest

The authors declare no competing financial interest.

Author contributions

Manuscript writing and editing (YD, ESJ). Both authors have made a significant contribution to this study and have approved the final manuscript.

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