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Exploring Nodular Lymphocyte Predominant Hodgkin Lymphoma: A Unique Subtype with Distinct Clinical and Pathological Traits

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Abstract

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an uncommon form of Hodgkin lymphoma (HL) that is characterized by its distinct morphology, typically affects older individuals, and has a lower incidence of mediastinal involvement. It is also associated with a higher relapse rate and a better prognosis compared to classical Hodgkin lymphoma (CHL). Unlike CHL, the tumor cells in NLPHL, known as LP cells, usually retain a B cell phenotype and do not express CD30. Due to the rarity of this subtype, limited research is available. In this study, we present a series of 10 cases of NLPHL diagnosed at our institution over a span of 10 years. The cases were retrospectively analyzed and classified based on morphological features and immunophenotypic patterns. Prognostic factors were also investigated. Our findings showed a predominance of peripheral lymph node involvement and generally favorable outcomes. In addition, two unusual cases were identified: one involving NLPHL associated with Rosai-Dorfman disease (RDD) and the other a composite lymphoma containing both NLPHL and diffuse large B cell lymphoma (DLBCL) components.

Keywords: Nodular lymphocyte predominant Hodgkin lymphoma, NLPHL, Special NLPHL cases, NLPHL case study, Composite lymphoma

Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare form of Hodgkin lymphoma (HL) that is distinguishable from classical Hodgkin lymphoma (CHL) based on its unique clinical, histological, and immunophenotypic features. These differences justify its classification as a separate entity in the World Health Organization (WHO) classification of hematolymphoid disorders [1-3]. While CHL accounts for about 95% of all HL cases, NLPHL represents the remaining 5% [4]. Both forms of lymphoma share a similar appearance of sparse neoplastic cells within a reactive background, but the characteristics differ significantly. In CHL, the presence of mononuclear Hodgkin cells and Reed-Sternberg (RS) cells—often multinucleated—are observed against a background rich in lymphocytes, histiocytes, plasma cells, and other inflammatory cells. In contrast, NLPHL has a distinctive nodular structure, where large neoplastic B cells (known as lymphocyte-predominant or LP cells) are surrounded by a predominance of small, reactive B cells. These LP cells, once referred to as “popcorn cells” or “L&H cells,” arise from germinal center B cells and undergo somatic hypermutation, expressing varying levels of B-cell markers [5]. They are typically encircled by T-cells, which are often CD57-positive.

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Clinically, NLPHL predominantly affects peripheral lymph nodes and tends to be diagnosed at an earlier stage compared to CHL. It is more commonly found in individuals between the ages of 30 and 40, with a male-to-female ratio of 3:1, and it has less frequent mediastinal involvement (about 15%). Additionally, NLPHL patients have a lower incidence of risk factors typically associated with HL [6].

Immunophenotypically, the RS cells in all CHL subtypes exhibit common characteristics, such as reduced expression of B-cell antigens (CD20, CD79a) and positive staining for CD30 and CD15. PAX5 is usually weakly expressed. On the other hand, LP cells in NLPHL generally maintain their B-cell phenotype and lack CD30 expression. These cells may express EMA and BCL6 in varying degrees. Typically, these LP cells reside within a mesh of follicular dendritic cell (FDC) processes that are filled with reactive B lymphocytes and histiocytes. Several rare morphological variations of NLPHL have also been documented.

Fan *et al.* [7] described six distinct morphological patterns of NLPHL, which are included in the WHO's current classification. These patterns include: (A) classic B-cell-rich nodular, (B) serpiginous/interconnected nodular, (C) nodular with significant extranodular LP cells, (D) T-cell-rich nodular, (E) diffuse T-cell-rich pattern (resembling TCRBCL), and (F) moth-eaten B-cell-rich pattern. Furthermore, mixed patterns were found to be more common than pure ones, and the diffuse T-cell-rich pattern (TCRBCL-like) was identified as a significant independent factor for predicting the recurrence of the disease.

In a study by Hartmann *et al.* [8], the impact of various morphological patterns in NLPHL was further examined. They found that cases where lymphoma cells were found outside the B-cell nodules—specifically in patterns C, D, E, and F—were strongly correlated with a higher risk of advanced stages and increased relapse rates.

The most common treatment for NLPHL involves field radiotherapy. While NLPHL generally progresses slower than classical Hodgkin lymphoma (HL), it is prone to frequent relapses. However, its prognosis remains more favorable compared to HL, with patients often experiencing high survival rates [5].

One of the major concerns in NLPHL is its potential transformation into diffuse large B-cell lymphoma (DLBCL), with studies showing transformation rates between 3-10% [9, 10]. According to the WHO, the transformation risk is between 3-5% [4]. A long-term study by Kenderian *et al.* [10] found that 7.6% of patients (17 out of 222) developed DLBCL, with a median transformation time of 35 months. This transformation was notably associated with prior chemotherapy treatments and splenic involvement at diagnosis. Genomic research on NLPHL reveals that the neoplastic LP cells rarely display monoclonal immunoglobulin gene rearrangements, but these become evident when the condition transforms into DLBCL.

In our study, we reviewed 10 NLPHL cases diagnosed in our institution over the last decade, and here we present a brief overview of these cases.

Materials and Methods

We retrospectively analyzed 10 NLPHL cases diagnosed between 2010 and 2020. We examined their morphological patterns and immunophenotypic characteristics, looking for correlations between these patterns and patient outcomes. Two experienced pathologists independently reviewed and categorized the cases based on established morphological criteria, following the guidelines set by Fan *et al.* [7]. Immunohistochemical staining was performed as needed. Clinical information, including diagnosis dates, treatment methods, recurrence rates, and final follow-up outcomes, was collected from patient records and hospital documentation.

Results and Discussion

Across a span of ten years, ten instances of Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) were diagnosed. The clinical and pathological data for these cases are displayed in **Table 1**. The male-to-female distribution was 6:4. Ages ranged between 8 and 80 years, with the average age being 35 years. Nine out of the ten patients had involvement of peripheral lymph node groups, with cervical nodes being the most commonly affected (3 out of 9). A single case involved a central lymph node group, specifically the mesenteric nodes.

7 of the 10 cases exhibited single, distinct morphological patterns. Pattern A and pattern C were each seen in three patients, while pattern E was found in one. The remaining three cases presented with a combination of morphological patterns, where pattern C was dominant in two cases, and pattern A in one.

Table 1. Clinical and pathological features of NLPHL cases

Case no.	Age/Sex	Lymph node site	Histological pattern	Year diagnosis and follow-up duration	Clinical outcome
1	12/M	Left cervical	C (85%) with minor E (15%)	2010	Follow-up data not available
2	16/M	Cervical	C (80%) and B (20%)	2013 (7 years)	Treated with chemotherapy; no recurrence to date
3	10/M	Right cervical	Pattern A	2017 (3 years)	Underwent chemotherapy; remains healthy
4	35/F	Axillary	A (45%), B (30%), and D (25%)	2017 (2 years)	Received chemotherapy; passed away in May 2019
5	80/M	Right submandibular	Pattern C	2017 (2 years)	Surgery only; no treatment; well until 2019
6	41/F	Left submandibular	Pattern A	2017 (3 years)	Surgery only; no recurrence to date
7	55/M	Right axillary	Pattern A	2018 (2 years)	Received chemo and radiotherapy; doing well
8	8/F	Right inguinal	Pattern C	2018 (9 months)	Died within 9 months due to septic shock
9	33/F	Mesenteric	Pattern C	2019	Follow-up information unavailable
10	23/M	Right supraclavicular	Pattern E	2020 (6 months)	Treated with chemotherapy; currently well

7 cases showed pure morphologic patterns, including pattern A and pattern C in 3 cases each, and pattern E in 1 case (**Figures 1a-1f**). Three cases showed mixed patterns (**Table 1**), with pattern C being the predominant pattern in 2 cases and pattern A in 1 case.

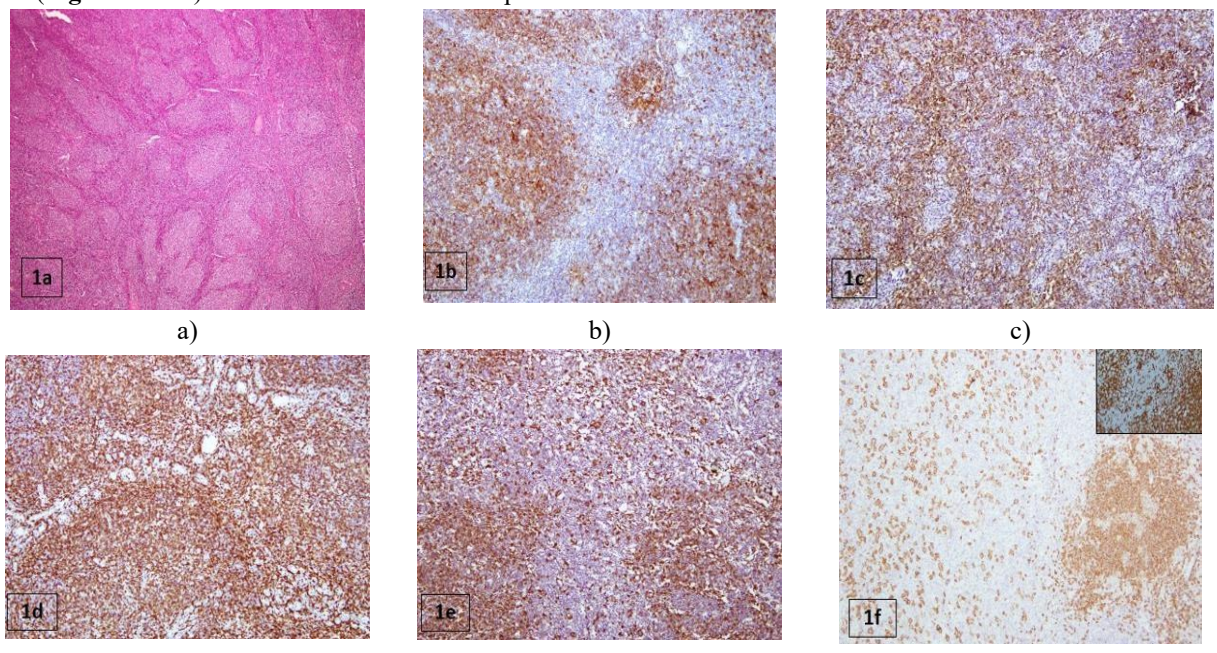


Figure 1. a) nodular pattern of NLPHL (H&E, 40X), b) nodular pattern (CD20, 100X), c) serpiginous pattern (CD20, 100X), d) T cell rich nodule (CD3, 100X), e) Nodules with prominent extra nodular L &H cells (CD20, 100X), and f) scattered large tumor cells in the diffuse background with preserved follicle at the periphery, pattern E (CD20, 100X), inset shows CD3 collar (200X).

On immunohistochemistry (IHC), CD20 consistently stained the LP cells in all cases (10/10). T-cells, positive for CD3, were observed forming a collar around the neoplastic LP cells in all cases. Most cases were negative for CD30 (8/10 cases) and CD15 (9/10 cases). However, a few tumor cells in some cases exhibited weak staining

for CD30 and CD15. Other IHC markers such as PAX5, EMA, and BCL6 were also valuable in confirming the diagnosis of NLPHL. Consequently, the IHC profile in all cases supported the NLPHL diagnosis. Information about the specific IHC markers used is detailed in Table 2. Bone marrow biopsy reports were available for 4 cases, and none showed any disease.

Table 2. Immunohistochemistry panel

Case No.	CD20	PAX5	EMA	BCL6	CD30	CD15	CD3 COLLAR
Case 1	+	+	+	+	-	-	+
Case 2	+	+S	-	-	-	-	+
Case 3	+	+W	-	+D	-	-	+
Case 4	+	+S	+	+D	+F	Few	+
Case 5	+	NA	-	NA	-	-	+
Case 6	+	+F	+S	+	-	-	+
Case 7	+	+S	+S	NA	-	-	+
Case 8	+	+S	-	NA	+W	-	+
Case 9	+	+S	+S	-	-	-	+
Case 10	+	+	+	+W	-	-	+

S = strong, W = weak, D = diffuse, F = focal, NA = not available

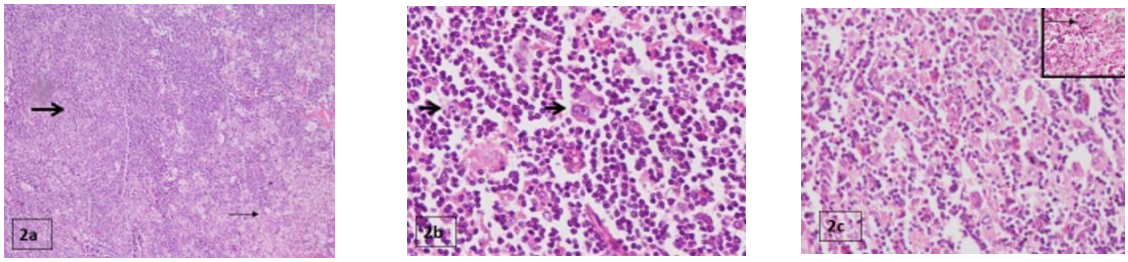
Two cases from the series were especially notable. In one case, NLPHL was present in one axillary lymph node, while diffuse large B-cell lymphoma (DLBCL) was found in another ipsilateral axillary lymph node, a condition known as composite lymphoma. In another case, both NLPHL and Rosai-Dorfman disease (RDD) were found within the same submandibular lymph node. These two cases were particularly unique.

Follow-up information was available for 8 patients. Two of these patients had died, while the remaining 6 were alive with no recurrence at the time of follow-up. The follow-up periods ranged from 9 months to 7 years, with an average follow-up of 21 months.

NLPHL is a distinct form of Hodgkin lymphoma (HL) with unique clinical features, a different treatment approach, and better overall patient outcomes. It tends to affect men more frequently than women, as observed in this study, although the small sample size limits definitive conclusions regarding gender prevalence. Most cases of NLPHL involve peripheral lymph nodes, which was also the case in this study. The majority of cases (9/10) involved lymph nodes in the cervical, submandibular, axillary, and supraclavicular regions.

Histologically, NLPHL is characterized by well-defined nodules visible at low magnification. A study of 137 biopsy samples by Fan et al. [7] found that pattern A was the most common, both as a pure pattern (54/137) and as the predominant pattern (31/137). Mixed patterns were more frequently seen than pure patterns. In our study, all cases with pure patterns showed nodular morphology, and this was the predominant pattern in lymph nodes with mixed patterns. However, pure patterns were more commonly observed in this study than mixed patterns (7 cases vs. 3 cases), which contrasts with Fan et al.'s findings [7].

A multivariate analysis by Hartmann *et al.* [8] found that histopathological variants of NLPHL were significantly linked to advanced disease stages and higher relapse rates. The study also identified variant histology as an independent prognostic factor for progression or relapse. Our study included a case (case 8) that displayed pattern C (variant histology) with a higher frequency of LP cells in the background population. These LP cells exhibited marked lobulation with prominent nucleoli compared to other cases. Sadly, this patient passed away within 9 months due to septic shock (**Figure 2**).



a) b) c)

Figure 2. a) (case no. 8) LP cells showing marked lobulation with prominent nucleoli (H&E 400X), b) LP cells

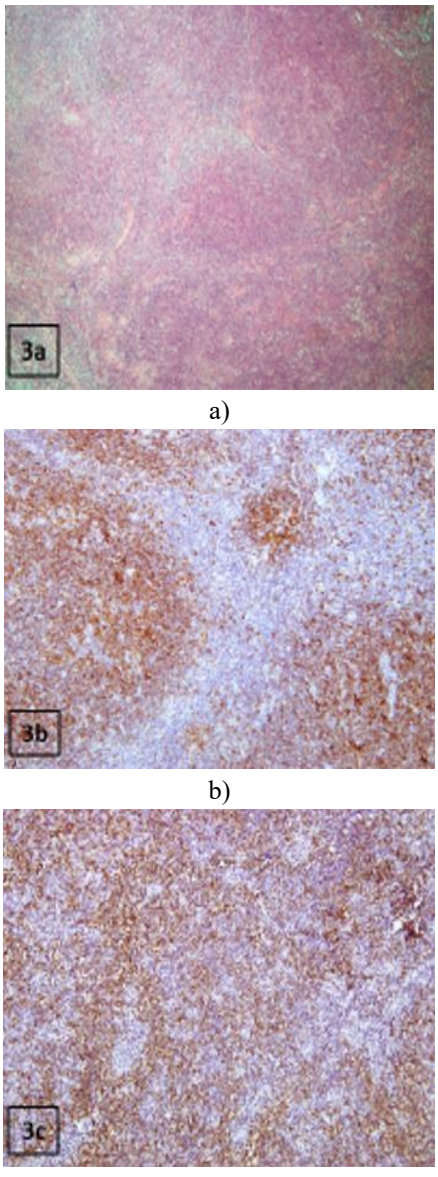
are positive for CD20 (400X), and c) collar of CD3 positive T cells surrounding LP cells (400X).

NLPHL is often differentiated from T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), but it generally has a good prognosis, despite occasional relapses. Research suggests that certain histopathological variants of NLPHL (patterns C, D, E, and F) correlate with higher rates of relapse and more advanced stages of the disease. Bone marrow involvement is rare, though stage 4 disease has a poor prognosis.

NLPHL can progress into diffuse large B-cell lymphoma (DLBCL) in relapse cases, with transformation occurring in approximately 3% to 10% of patients. Eyre et al. [11] found that the median time for transformation is about 5 years and 33 days, but this duration varies across cases. Transformation is more likely in patients with extranodal involvement, particularly in the liver, spleen, and bone marrow. Compared to de novo DLBCL, patients who experience transformation show a higher incidence of bone marrow involvement ($P = 0.013$). Transformation generally results in poorer outcomes.

There is no single treatment protocol universally accepted for NLPHL. The general approach, however, leans toward conservative management rather than aggressive treatment. The NCCN guidelines recommend site-specific radiation therapy (ISRT) for early-stage favorable disease. For early-stage unfavorable disease and advanced-stage NLPHL, an ABVD/CHOP regimen combined with ISRT is suggested. Rituximab may be considered as an adjunct to ABVD/CHOP. For refractory cases, maintenance rituximab may be considered. A biopsy is advised during relapse to check for potential transformation into aggressive B-cell lymphoma [12-14].

Two unusual cases in our study require special mention. One case (case 6, Table 1) involved both NLPHL and Rosai-Dorfman disease (RDD) present within the same lymph node. These diseases were located in adjacent regions of the node and were easily distinguishable from one another. The RDD area showed histiocytes positive for S-100 but negative for CD1a, while the NLPHL region displayed the typical nodular morphology and the characteristic IHC features of L&H cells. Many case reports describe RDD in conjunction with lymphoma, often affecting different anatomical sites. However, only a few report the simultaneous occurrence of RDD and HL in the same lymph node. After lymph node excision, the patient received no additional treatment and has been healthy for the past 3 years. This co-occurrence should be considered by pathologists, as it could complicate diagnosis, particularly in small or needle biopsies. Nonetheless, it does not affect prognosis or treatment plans, which should be based on the lymphoma type (**Figure 3**).



a)

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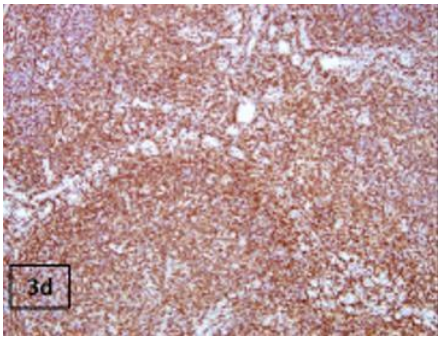

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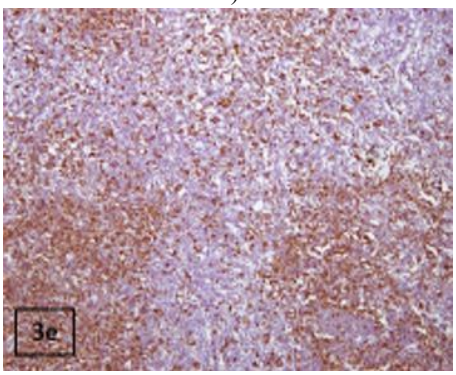

e)

Figure 3. a) (case no. 6) effacement of nodal architecture by a tumor (thick arrow) interspersed with paler histiocytic areas (thin arrow) (H&E 100X), b) tumor comprising mononuclear LP cells with prominent nucleoli (arrows) (H&E 400X), c-e) in pale areas, cells were arranged in loose sheets and clusters with histiocytes showing emperipolesis (inset, arrows) (H&E 400X).

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Conclusion

Two unusual cases in our study require special mention. One case (case 6, **Table 1**) involved both NLPHL and Rosai-Dorfman disease (RDD) present within the same lymph node. These diseases were located in adjacent regions of the node and were easily distinguishable from one another. The RDD area showed histiocytes positive for S-100 but negative for CD1a, while the NLPHL region displayed the typical nodular morphology and the characteristic IHC features of L&H cells. Many case reports describe RDD in conjunction with lymphoma, often affecting different anatomical sites. However, only a few report the simultaneous occurrence of RDD and HL in the same lymph node. After lymph node excision, the patient received no additional treatment and has been healthy for the past 3 years. This co-occurrence should be considered by pathologists, as it could complicate diagnosis, particularly in small or needle biopsies. Nonetheless, it does not affect prognosis or treatment plans, which should be based on the lymphoma type.

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