The Prevalence and Importance of Variant Patterns in Nodular Lymphocyte Predominant Hodgkin Lymphoma

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Abstract: Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a rare type of B-cell lymphoma with good prognosis and distinct clinicopathologic features. The hallmark histological feature is the presence of malignant lymphocyte predominant (LP) cells embedded within nodules predominantly composed of small B-lymphocytes. Immunoarchitectural variations from these classic nodules could occur. The clinical and pathological significance of NLPHL with variant patterns is, however, uncertain and controversial. Some oncologists and pathologists consider variant atypical nodules to represent a simple localized overgrowth of the LP cells without significant pathological or clinical implications. Other oncologists, however, suggest that they might represent a different biological behavior in the form of intranodal progression with early transformation into large B-cell lymphoma. Therefore, NLPHLs with variant atypical patterns represent a more aggressive clinical course and an indicator of a higher risk of recurrence that warrants a more aggressive treatment even in the early stages.

We performed a retrospective review study to investigate the prevalence and importance of atypical nodules in NLPHL. We found seven cases of NLPHL, three (43%) of which showed variant patterns with different immunoarchitectural features from the classic nodules of NLPHL. We did not find clinical or prognostic differences between the two groups of classic nodules of NLPHL and atypical variant nodules of NLPHL. The significance of which, however, cannot be drawn from this small case series. Therefore, further larger scale studies are warranted. In addition, pathologists should be aware of this phenomenon to avoid overcalling these cases as high-grade lymphomas.

Keywords: Nodular lymphocyte predominant Hodgkin lymphoma, atypical nodules, variant patterns, transformation, large B-cell lymphoma.

INTRODUCTION

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) constitutes 3-5% of Hodgkin lymphoma (HL) [1, 2]. The hallmark histological feature is the presence of malignant CD20 positive lymphocyte predominant (LP) cells embedded within nodules composed of small B-lymphocytes [1]. NLPHL is currently considered a B-cell lymphoma of germinal-center origin with a good overall prognosis [1, 3, 4]. However, recurrence could occur and transformation into large B-cell non-Hodgkin lymphoma (NHL) has been reported with an incidence of 2-3% [1, 5, 6]. Variations from the usual classic nodules of NLPHL can occur, the prevalence and significance of which is, however, not yet resolved [2, 7]. We performed a retrospective review study to investigate the prevalence and importance of aberrant nodules in NLPHL.

MATERIALS AND METHODS

A computer-based search was used to retrieve all cases of NLPHL that were diagnosed in our institution over the past five years. For each case, sections of 4-6 µm thickness were stained with routine hematoxylin and eosin (H&E) stain and one H&E stained slide for each block was prepared. The retrieved cases were divided into NLPHL with classic conventional nodules and NLPHL with any aberrant variant nodules. The histologic features were compared for each case. We compared the size, shape and location of the nodules as well as their demarcation from the surrounding lymphoid tissue. We also compared the nature of the neoplastic cells within the nodules along with the lymphocytic background and the pattern of the epithelioid histiocytes within the nodules.

Based on the initial microscopic examination, immunohistochemistry (IHC) panel was conducted with the following available markers: CD45 (LCA), CD20, CD79a, CD30, CD15, CD3, CD10, CD23, CD21, bcl2, bcl6, EMA (Epithelial Membrane Antigen), EBV-EBER (Epstein Barr Virus) and Ki67 (Dako, Glostrup, Denmark). IHC study was performed on the formalin-fixed, paraffin-embedded blocks with the above primary antibodies using a standard automated streptavidin-biotin-peroxidase detection system (Dako, Glostrup, Denmark) with microwave antigen-retrieval. Positive and negative controls were run in parallel for every stain.

For each case relevant clinical features were also collected. They included the age, gender, anatomical location and size of the involved lymph nodes, the clinical symptoms along with the disease stage, the received therapy and follow up and survival data.

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Table 1: Comparison of the Pathological and Clinical Features Between the Four Cases of Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) with Classic Nodules and the Three Cases of NLPHL with the Atypical Nodules

Features	Classic NLPHL nodules (4)	DLBCL-like atypical nodules (1)	TCRBCL-like atypical nodules (2)
1) Histologic features:			
Size	Variable (small, medium to large)	Medium to large	Large
Shape	Uniform round to oval	Irregular round, oval and serpinginous	Uniform round
Demarcation	Can be vague or well-demarcated by eosinophilic thin rim of histiocytes	Well-demarcated by dark thick ring of small lymphocytes	Can be vague or well-demarcated by thin or thick layer of hyaline collagen fibers
Location	Peripheral and central	Peripheral and central	Central
Neoplastic cells	Scattered and rare LP cells (1% of nodule population)	Dominant large pleomorphic cells (>90% of nodule population)	Frequent and scattered, but not dominant (10% of nodule population)
Small lymphocytes	Dominant (>90% of nodule population)	Scattered (5-10% of nodule population)	Dominant (90% of nodule population)
Epithelioid histiocytes	Scattered inside the nodule (form eosinophilic ring between nodules)	Larger number inside the nodule (contribute to the eosinophilic center of the nodule)	Moderate number inside the nodules (contribute to the starry sky-like pattern)
CD20	Few scattered positive LP cells	Solid sheet of large number of large B-cells	Frequent, but scattered individual cells
CD3	Scattered T-cells population	Less T-cells population in the DLBCL-like nodules	Predominant T-cells population
CD3-Rosette	Maintained around LP cells	Partly maintained around large B-cells	Lost
CD21/CD23	Maintained residual FDC	Absent FDCs	Maintained residual FDCs
EMA	Negative	Negative	Positive
bcl 6	Negative	Positive	Positive
CD10	Negative	Few large cells were positive	Negative
EBV	Negative	Negative	Negative
Ki67	Low (3%)	Increased (40%)	Slightly increased (10%)
2) Clinical features:			
M:F	3:1	F	1:1
Age (years)	24, 27, 35: 20	43	60:21
Location	Left (3) and right (1) cervical	Right cervical	Left axilla, right cervical
Presentation	Lymphadenopathy for 3 to 5 months	Lymphadenopathy for 3 months	Lymphadenopathy for 4 months and 8 months
B-symptoms	No B-symptoms	No B-symptoms	No B-symptoms
Size	3.0 to 4.5 cm	4.0 cm	5.0 cm, 4.0 cm
Stage	Stage I (3): Stage II (1)	Stage I	Stage I
Therapy	RT (3): RT+ABVD (1) - 3 cycles	R-CHOP - 6 cycles	ABVD - 4 cycles : RT+ABVD - 3 cycles
Survival	Alive without recurrence (5.5 to 7 years)	Alive without recurrence (4 years)	Alive without recurrence (2.5 and 3.5 years)

DLBCL: diffuse large B-cell lymphoma, TCRBCL: T-cell rich B-cell lymphoma, LP: lymphocyte predominant, FDCs: follicular dendritic cells, EMA: epithelial membrane antigen, EBV: Epstein Barr Virus, M:F, male to female ratio, RT: radiotherapy, R-CHOP: Rituximab + Cyclophosphamide, Adriamycin, Vincristine and Prednisone, ABVD: Adriamycin, Bleomycin, Vinblastine and Dacarbazine.

The medical file for each patient was retrieved and reviewed thoroughly to collect the above clinical data for each case. The retrieved cases were divided into three groups and the histological and clinical features of the three groups were tabulated for comparison in Table **1**.

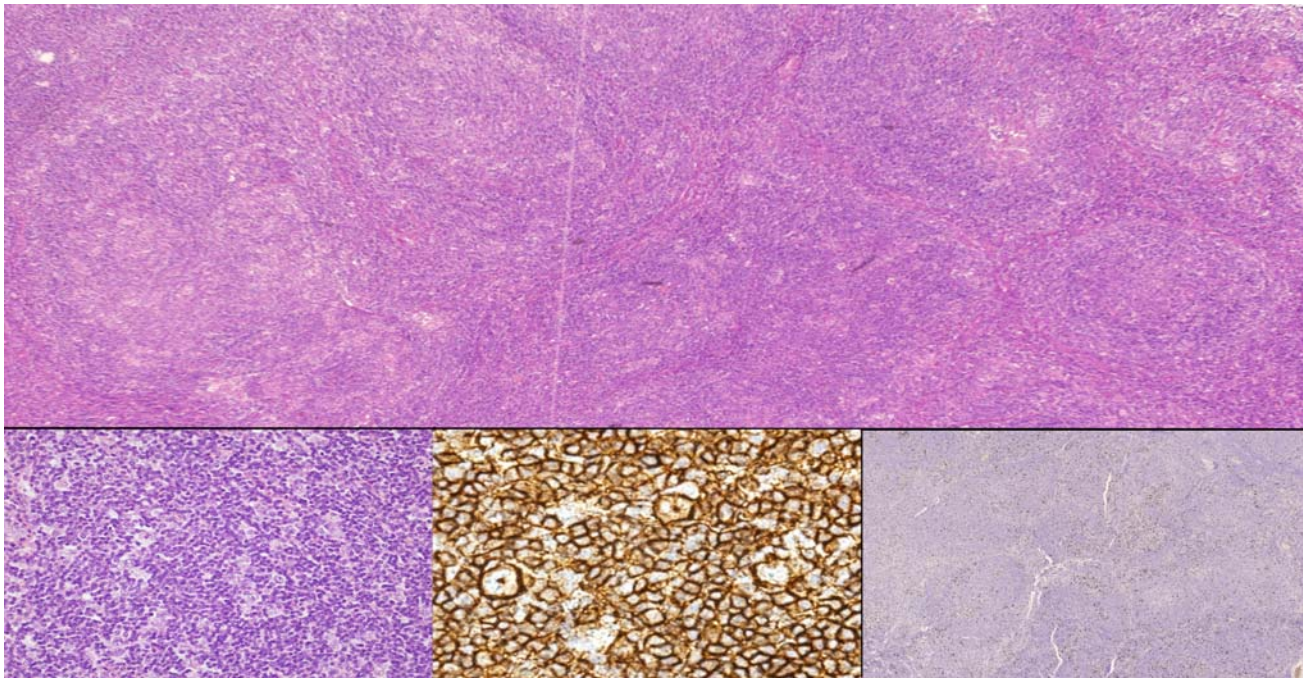

Figure 1: The classic nodules of NLPHL (Hematoxylin and eosin (H&E) stain, original magnification x40). Left inset shows a typical nodule of NLPHL composed of small mature lymphocytes punctuated by large LP cells with a starry sky appearance (H&E stain, original magnification x400). Middle inset shows CD20 positive LP cells in a background of small CD20 positive B-lymphocytes (Monoclonal, Dako, Glostrup, Denmark; original magnification x400). Right inset shows low Ki67 proliferation index (Polyclonal, Dako, Glostrup, Denmark: original magnification x200).

RESULTS

We retrieved seven cases of NLPHL. Four cases showed the classic nodules of NLPHL with the typical immunoarchitectural pattern of scattered CD20 positive LP cells and a background of small CD20 positive lymphocytes (Figure **1**).

Three cases (43%) showed, in addition to the classic nodules of NLPHL, foci of enlarged nodules with different immunoarchitectural patterns (Table **1**). One case showed frequent nodules composed of sheets of large pleomorphic neoplastic lymphoid cells (Figure **2**). CD45 (LCA) and CD20 stained the large cells and the background small lymphocytes (Figure **2**). CD79a and bcl6 stained the large cells. CD30, CD15, bcl2 and EBV were negative. CD10 stained few large cells in these nodules. CD57 showed nesting pattern around the large cells in the classic nodules and in the atypical nodules. Ki67 proliferation index was low (3%) in the classic nodules and was increased (40%) in the atypical nodules (Figure **2**). CD21 and CD23 were negative in the atypical nodules suggesting complete absence of the follicular dendritic cells (FDCs).

The other two cases showed foci of well-defined expanded nodules surrounded by collagen bundles (Figure **3**). These nodules showed frequent large lymphoid cells within a background of small T-lymphocytes (Figure **3**). The large lymphoid cells were positive for LCA, CD20, CD79a, bcl6, EMA and CD30. They were negative for CD15, ALK, CD10, bcl2 and EBV. CD23 and CD21 were absent in these aberrant nodules. CD3 showed a dominant background of small T-lymphocytes in these nodules (Figure **3**) in contrast to the B-lymphocytes dominant background in the adjacent classic nodules (Figure **1**). Ki67 proliferation index was 10% in these atypical nodules (Figure **3**).

We reported the three cases as NLPHL with variable histological features. One case had diffuse large B-cell lymphoma-like nodules (DLBCL) and received R-CHOP (Rituximab, Cyclophosphamide, Adriamycin, Vincristine and Prednisone) treatment. The other two cases had T-cell rich B-cell lymphoma-like nodules (TCRBCL). One received ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) chemo-therapy and the other had combined radiotherapy (RT) and ABVD. Three patients with classic NLPHL received RT, and the fourth patient received ABVD (Table **1**). All patients presented with early-localized disease. All patients were disease free and alive after a follow up period that ranged between 2.5 and 7 years. We did not find major clinical or prognostic differences between the three groups (Table **1**).

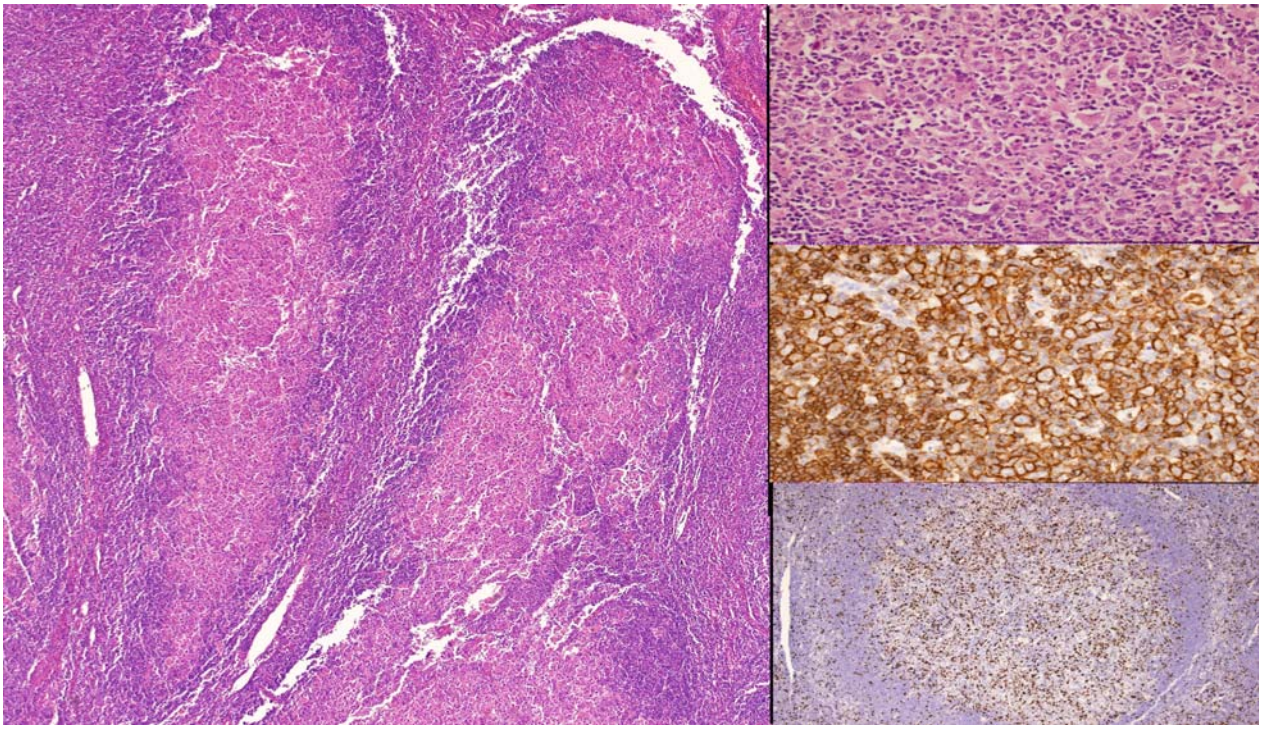

Figure 2: Enlarged atypical well-demarcated nodules with eosinophilic centre and a dark thick ring (H&E stain; original magnification x40). Upper inset shows a diffuse sheet of large pleomorphic cells with abundant eosinophilic cytoplasm and large vesicular mononuclear and multinucleated nuclei with prominent nucleoli. The background shows scattered small lymphocytes (H&E stain, original magnification x400). Middle inset shows a diffuse sheet of large CD20 positive lymphoid B-cells (Dako, original magnification x400). Lower inset shows increased Ki67 proliferation index in the large atypical nodule (Dako, original magnification x100).

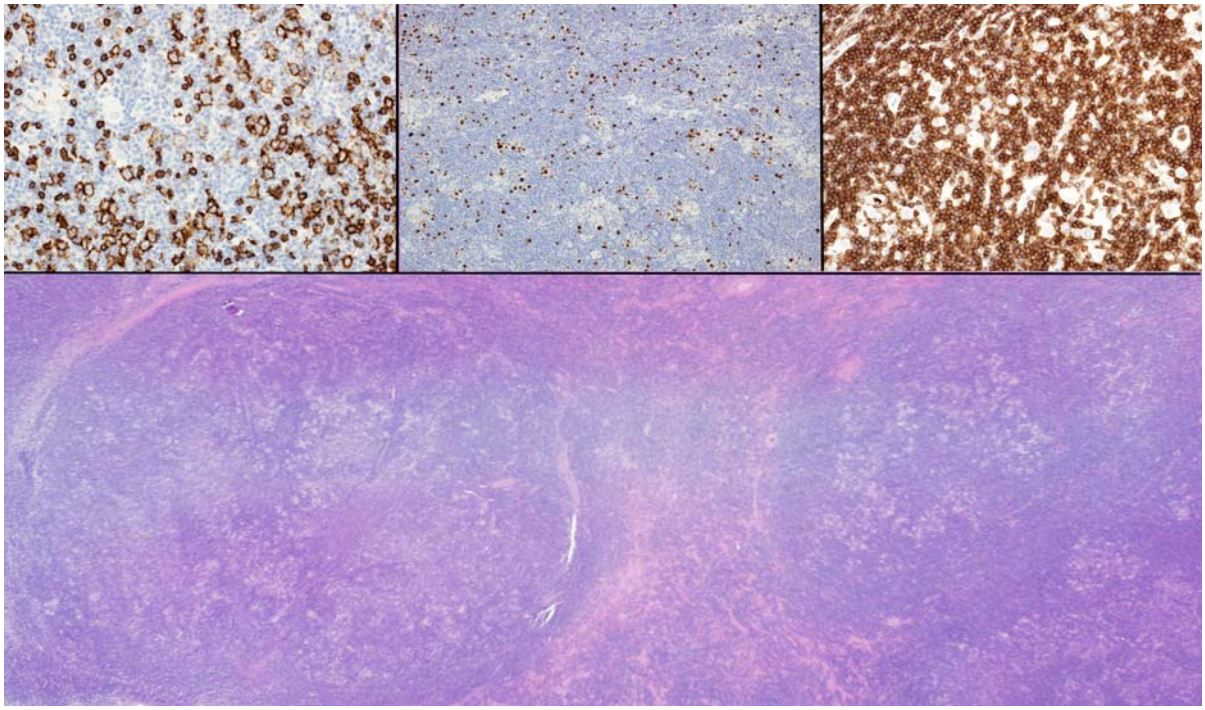

Figure 3: Enlarged atypical nodules demarcated by thin hyaline borders and composed of predominantly small lymphocytic cells punctuated by a starry sky appearance formed by large eosinophilic lymphoid cells (H&E stain, original magnification x20). Left inset shows large CD20 positive neoplastic cells and scattered small CD20 positive lymphocytes in the background (Dako, original magnification x200). Middle inset shows slightly increased Ki67 proliferation index (Dako, original magnification x100). Right inset shows predominantly CD3 positive small T-lymphocytic background punctuated by large negative neoplastic cells (Dako, original magnification x400).

DISCUSSION

The exact etiology and pathogenesis of NLPHL are still controversial. NLPHL is considered a germinal-center derived B-cell lymphoma [2, 3, 5]. NLPHL is considered to be more linked to B-cell NHL rather than being a variant of HL [2, 3, 5]. The neoplastic LP cells have been demonstrated to originate from the germinal-center B-cells [3,5]. Several hypotheses suggest a link between NLPHL and progressive transformation of germinal centers (PTGC) [8]. PTGC is considered a precursor lesion for NLPHL [8]. Documented cases of concurrent or subsequent transformation of NLPHL into large B-cell lymphoma were reported more in NLPHL than in HL, with an overall incidence of 2-3% [6]. In contrast to classic HL, EBV has no role in the pathogenesis of NLPHL [3, 5]. Variations from the classic nodules of NLPHL in the form of nodules with different immunoarchitectural patterns do occur, albeit rare [2, 4, 7]. Fan et al. [7] subclassified the nodules of NLPHL into six categories on the basis of immunoarchitectural patterns as follows: 1) classic (small B-cell rich) nodular; 2) serpinginous, interconnected nodular; 3) nodular with extranodular lymphocytic and histiocytic (L&H) cells; 4) (small T-cell rich) nodular; 5) diffuse (T-Cell Rich B-Cell Lymphoma-like (TCRBCL-like) and 6) diffuse (Large B-Cell Lymphoma-like (DLBCL-like). The TCRBCL-like and the DLBCL-like atypical nodules could suggest early intranodal transformation of NLPHL into higher-grade large B-cell lymphoma [2]. They may explain the progression of 5% of NLPHL cases into large B-cell lymphoma [2, 6, 7]. Some suggested a sequence of events that explain the occurrence of these atypical nodules and their progression into large B-cell lymphoma. Atypical follicular hyperplasia (PTGC) progresses into classic NLPHL nodules which develop into either TCRBCL-like nodules or DLBCL-like nodules which ultimately transform into DLBCL [3, 5, 8]. NLPHL is not a static disease process, but rather a dynamic lymphoid malignancy with a tendency for concurrent or subsequent transformation into large B-cell lymphoma [3, 5, 6, 8].

The optimal treatment for NLPHL is also controversial. Early stage classic NLPHL is usually a localized disease with excellent prognosis, and patients either receive RT alone or combined RT and chemotherapy [1, 6]. For a higher stage disease, a more aggressive chemotherapy approach is agreed by most oncologists [2, 9]. For the early stage NLPHL, but with variant pathologic patterns, some oncologists advocate a more aggressive chemotherapy approach. They recommend R-CHOP regimen, on the basis that these cases are at a higher risk of transformation into a high grade large B-cell lymphoma or are more likely to recur and relapse in the future [2, 4, 9].

In our study, we did not find significant clinical or prognostic differences between the classic NLPHL cases and the other NLPHL cases with the atypical nodules. However, our study is limited because it is a small case series. Therefore the clinical or prognostic importance of the variant patterns cannot be drawn from the small number of the cases studied. We recommend a larger scale study to investigate the prognostic and therapeutic implications of these atypical nodules in NLPHL.

In conclusion, variant nodules in NLPHL are not uncommon and might present a diagnostic challenge for the pathologists. They could lead to misinterpretation of NLPHL as a high grade lymphoma with unnecessary more aggressive treatment. The clinical and prognostic significance of these atypical nodules in NLPHL as well as the best acceptable management of these cases are, however, controversial and uncertain. This needs to be validated by a larger scale study.

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