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Nodular Lymphocyte Predominant Hodgkin Lymphoma- A Retrospective Immunohistochemical Study of Patients in Bangalore, Karnataka

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Abstract
Nodular lymphocyte predominant Hodgkin lymphoma comprises 10% of HL and is considered to be an indolent lymphoma, but known for recurrences. Classically seen in middle age population, this lymphoma has a favourable prognosis, unless stage IV ensues, where bone marrow involvement is inevitable and prognosis becomes grim. This study emphasizes on the typical features of NLPHL, with male population being commonly affected. Also the reactive T cell population surrounding the LP cells are consistently positive for CD3 than CD5. LP cells are also positive for CD20, CD79a, CD45, PAX5, OCT-2 and BOB-1 while negative for CD10, CD30 and CD15. The study discusses already known facts of NLPHL with corroboration from previous studies.

Introduction

The category of Hodgkin lymphoma encompasses classical Hodgkin lymphoma (CHL) and the less common nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). Both CHL and NLPHL are characterized by large, neoplastic cells derived from germinal centre B cells, in an inflammatory background. NLPHL is a B cell neoplasm usually characterised by nodular or nodular and diffuse proliferation of small lymphocytes with single scattered large neoplastic cells (LP/L&H/Popcorn cells). NLPHL accounts for 10% of all Hodgkin lymphoma.

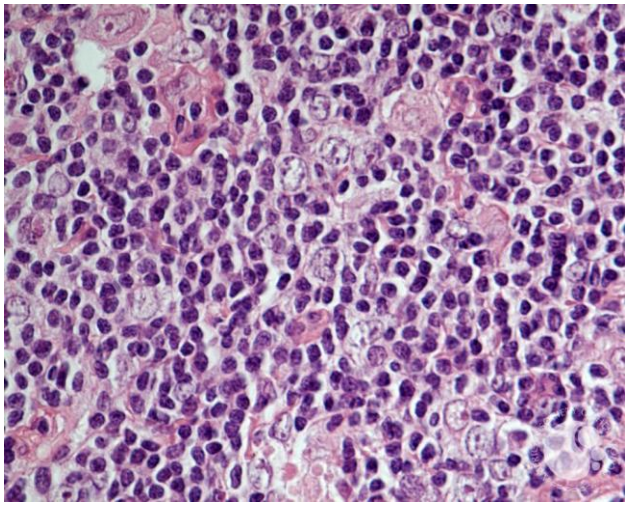
Clinically, NLPHL differs from CHL. In NLPHL, the classic scenario is a male patient with a single site of lymphadenopathy that has been slowly enlarging for months or years. Many patients present with very large solitary masses and no other signs or symptoms of lymphoma. NLPHL has a male predominance and typically presents in middle age (30-50 years). The most common sites of involvement are peripheral lymph nodes, including cervical, axillary, and inguinal. Mediastinal and retroperitoneal lymph node involvement is rare; a diagnosis of NLPHL in these locations should be made with caution. Mesenteric lymph node involvement can be seen unlike CHL. Bone marrow involvement is very uncommon,[4] but when stage IV disease ensues, the prognosis is poor[1]. Patients with advanced disease may have involvement of spleen, rare cases have destructive lytic lesions on the bone. Approximately 20% of patients present with advanced stage disease. NLPHL is clinically indolent but has a higher

recurrence rate than CHL; consequently, many patients die from therapy-related complications rather than from lymphoma[2]. As a result, the approach to therapy has changed. CHL is treated aggressively and NLPHL may be treated more conservatively, making accurate subclassification of Hodgkin lymphoma essential.

On gross examination, the involved lymph node is typically nodular and firm with a homogeneous, pale appearance. Microscopically, on low magnification, the lymph node architecture is effaced by large, often interlocking nodules. A rim of normal compressed lymph node is often present at the periphery. Unlike CHL, sclerosis between nodules is rare, but can occur in older lesions. There are 6 patterns described in NLPHL namely, Pattern A (Classical B cell rich nodular pattern), Pattern B (Serpiginous interconnected pattern), Pattern C (Prominent extra nodular L&H pattern), Pattern D (T cell rich nodular), Pattern E (Diffuse TCRBCL or DLBCL like) and Pattern F (Diffuse moth eaten, B cell rich pattern).

On higher magnification, the nodules in NLPHL are typically composed of small B lymphocytes and variable numbers of larger atypical cells. Admixed epithelioid histiocytes may be present. The large cells have lobulated nuclei (but may occasionally resemble classic Reed-Sternberg (RS) cells. The neoplastic cells in NLPHL were historically known as lymphocytic and histiocytic (L&H) cells, since they were believed to be histiocytes, although they are now known to be B cells. Owing to the uncanny resemblance to a kernel of popped corn, they have also often been termed popcorn cells. More recently, the preferred terminology is lymphocyte-predominant cells or LP cells [4]. In typical cases the LP cells reside in large nodular meshwork of follicular dendritic cell processes that are filled with non-neoplastic (mainly B) lymphocytes and histiocytes. There is increasing evidence that NLPHL cases with pure diffuse growth pattern overlap with T cell histiocytic rich B cell lymphoma (THRLBCL).

The most cost-effective panel of immunohistochemical stains includes CD3, CD20, CD15, CD30, and CD45. In the classic case, CD20 should highlight the large nodules on low magnification. This finding effectively excludes nodular sclerosis Hodgkin lymphoma. On higher magnification, CD20 and CD45 mark the LP cells. The LP cells are generally negative for CD30, although a small subset may be positive since CD30 is an activation marker. CD15 is not expressed on LP cells. CD3-positive T cells typically surround the LP cells, in two to three layers forming what are commonly referred to as T-cell rosettes in classic B cell rich pattern 3. The LP cells are ringed by CD279/PD1 positive T cells in most instances. LP cells are positive for CD75, OCT-2, BOB-1 and BCL-6. CD10 IHC is generally absent but can be seen in a few cases. EMA is positive in more than 50% of cases. In 9-27% of cases, LP cells are IgD positive, but are IgM negative.



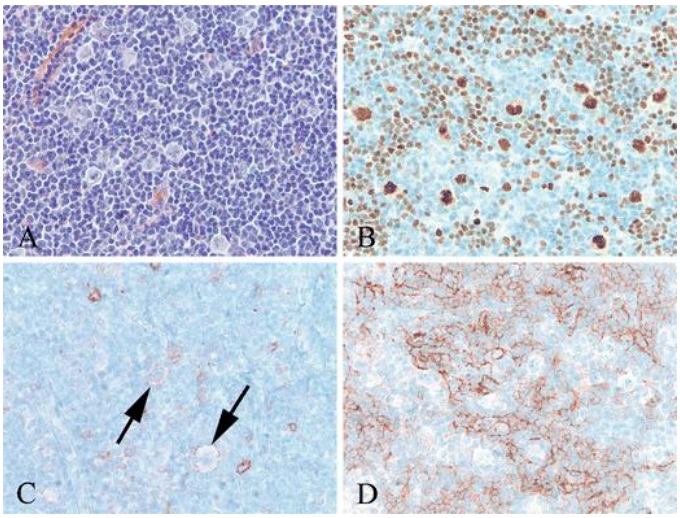
1.1: Histomorphology of NLPHL, with characteristic popcorn cell

Materials and Methods

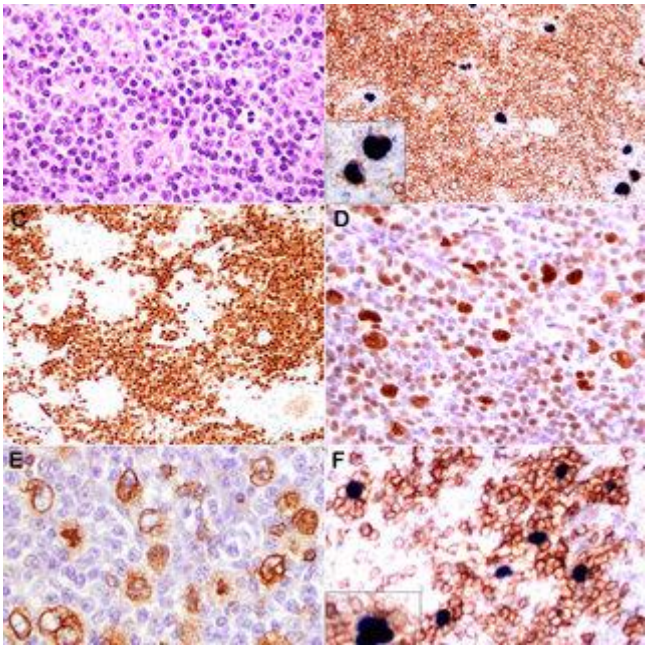
We retrospectively reviewed 24 cases of nodular lymphocyte predominant Hodgkin lymphoma from 2011- 2015. The blocks and slides were retrieved from the archives of pathology, reviewed by three expertonco-pathologists at KMIO.

Immunohistochemistry slides of the respective cases were also reviewed. Relevant clinical details like age, gender and site of the lymph node involvement were also collected. Antibodies used in immunohistochemical procedures included CD3

(clone SP7, rabbit, Lab vision, Fermont, CA), CD5 (Clone SP35, mouse, Ventana, Tucson, AZ), CD20 (clone L26, mouse: DAKO, Carinteria, CA), OCT-2 (clone ZO001, mouse, Thermo fisher Scientific), BOB-1(clone TG14, mouse, biocare medical), CD45 (clone D9M8I, rabbit, CST), CD30 (Ber-H2 clone, mouse, Sigma Aldrich), CD15 (clone H198, mouse, eBioscience), EMA (E29 clone, mouse, Novus Biologicals) and PAX5 (AV34686 clone, mouse, Thermo Fischer)



2.A: Histomorphology of NLPHL. 2.B: CD20 positivity in the LP cells and surrounding B cells. 2.C: PAX-5 positivity in the LP cells. 2.D: CD3 positivity in the reactive T cells forming rosettes.



3.A: Histomorphology of NLPHL. 3.B: CD45 staining in the LP cells. 3.C: CD79a staining in the LP cells. 3.D: OCT-2 staining in the LP cells. 3.E: BOB-1 staining in the LP cells. 3.F CD5 staining in the reactive T cells forming rosettes.

Statistical Analysis

Chi- squared tests of independence were performed to compare parameters. All statistical analyses were performed using R version 3.1. Results were considered statistically significant with $P < 0.05$.

Age	No.
10-20	3 (12.5%)
21-30	9 (37.5%)
31-40	7 (29.6%)
41-50	2 (8.3%)
51-60	11 (45.8%)
61-70	0 (0%)
71-80	1 (4.2%)

S. No	AGE	SEX	CD3	CD5	CD10	BCL2	CD15	CD30	OCT-2	BOB1
1	26	M	R	R	N	P	N	N	P	P
2	22	M	R	R	N	P	N	N	P	NEG
3	55	F	R	P	N	P	N	N	P	P
4	72	M	R	R	N	P	N	N	P	P
5	36	M	R	R	N	P	N	N	P	P
6	28	M	R	R	N	P	N	N	P	P
7	55	F	R	N	N	P	N	N	P	P
8	15	M	R	R	N	P	N	N	P	P
9	38	M	R	R	N	ND	N	FP	P	P
10	50	M	R	R	N	ND	N	N	P	P
11	36	M	R	N	N	P	N	P	P	P
12	33	M	N	N	N	P	N	N	P	FO-CAL P
13	29	M	R	N	N	P	N	N	P	P
14	50	M	R	N	N	P	N	N	P	P
15	25	F	R	N	N	ND	N	P	P	P
16	28	F	R	N	N	ND	P	P	N	P
17	28	M	R	N	N	P	N	N	P	P
18	16	M	R	N	N	P	N	N	P	P
19	29	M	R	N	N	P	N	N	P	P
20	32	M	R	N	ND	ND	N	N	P	P
21	21	M	R	N	ND	ND	N	N	P	P
22	16	M	R	N	ND	ND	N	N	P	P
23	33	M	R	N	ND	P	N	N	P	P
24	28	M	R	N	ND	ND	N	N	P	P

M: Male, F: Female, N: Negative, P: Positive, R: Reactive,
FP: Faint positive ND: Not done

IHC marker	Positive in LP cells	Negative in LP cells
CD20	24 (100%)	0 (0%)
CD79a	24 (100%)	0 (0%)
PAX5	24 (100%)	0 (0%)
CD45	24 (100%)	0 (0%)
CD10	18 (75%)	6 (25%)
CD15	1 (4%)	23 (96%)
CD30	4 (16%)	20 (84%)
OCT-2	23 (95%)	1 (5%)
BOB-1	23 (95%)	1 (5%)
BCL-2	16 (67%)	8 (33%)

Results

We identified 24 patients of NLPHL from 2011-2015. Patients were mostly young between 20-40 years (16/24, 66.67%). There was a distinct male preponderance (20/24, 83.3%), and was statistically significant (p=0.03). Most cases involved either cervical, axillary or inguinal lymph nodes, cervical lymph nodes being the most common (13/24, 54%). Immunohistochemical analysis and evaluation formed the integral part of the study. It was found that CD45, CD20, CD79a and PAX5 staining highlighted the LP cells in all twenty four cases, while OCT-2 and BOB-1 were highlighted in twenty three cases (95.8%) cases, which were considered statistically significant. Correlation with CD3 and CD5 IHC staining on T cell rosettes and background reactive T cells were examined, and it was seen that CD3 expression was far more consistent than CD5 expression in T cell rosettes and reactive T cells. Also it was seen that, those cases which were double positive for CD3 and CD5 constitutes only eight cases (8/24, 33.3%). Fifteen cases of NLPHL, which demonstrated CD3 positivity in the reactive T cells, simultaneously exhibited CD5 immunonegativity. None of the cases of NLPHL displayed CD10 positivity in the LP cells. Sixteen cases (66.6%) also showed bcl-2 positivity in the popcorn cells, but were not statistically significant (p=0.10). None of the cases showed IHC positivity for cyclinD1. EMA was done only in five cases, three (60%) of which showed IHC positivity in LP cells. EBV-LMP IHC was done only in eight cases, all showed negative nuclear staining. CD57 was done in two cases of NLPHL to flaunt the background T cells, both of which showed immunopositivity in the reactive T cells.

Discussion and Summary

This study evaluates the clinical characteristics and immunohistochemical properties of NLPHL. According to Carbone A et al[5], NLPHL is predominantly seen in adolescent age group with marked male preponderance, which is in coherence to our study. Study by Lee AI et al[6] elucidated that CD3 is a more consistent marker than CD5 in demonstrating surrounding reactive T cells in NLPHL which is in accordance to our study. CD45, PAX5, CD20, BOB-1 and OCT-2 are consistent immunohistochemical markers of LP cells according to Piccaluga PP et al[7], which was in concurrence to our study. According to Hawkes EA et al[8], CD10was immunonegative in all LP cells, which was in congruity to our study.

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