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

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ABSTRACT

BACKGROUND

The term Hodgkin's lymphoma includes classical Hodgkin lymphoma (CHL) and the less common nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). NLPHL is a B cell neoplasm usually characterised by nodular or follicular 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.

METHODS

This is a retrospective study. Histopathology slides and blocks of 24 cases of nodular lymphocyte predominant Hodgkin lymphoma were collected from the archives of histopathology from 2011 to 2015. The immunohistochemistry slides of the corresponding histopathology cases were also assembled. Both the slides were reviewed by three expert onco-pathologists and IHC markers were studied and compared.

RESULTS

Patients were mostly young between 20 and 40 years (16 / 24, 66.67 %). There was a distinct male preponderance (20 / 24, 83.3 %). Most cases involved cervical, axillary or inguinal lymph nodes, with cervical lymph nodes being the most common (13 / 24, 54 %). 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 %), which was statistically significant. 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 %).

CONCLUSIONS

CD3 is a more consistent marker than CD5 in demonstrating surrounding reactive T cells in NLPHL. CD45, PAX5, CD20, BOB - 1 and OCT - 2 are consistent immunohistochemical markers of LP cells.

KEYWORDS

Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL), Classical Hodgkin Lymphoma (CHL), Cluster Differentiation (CD), Lymphocyte Predominant Cells (LP Cells), Lymphocyte and Histiocytic Cell (L & H Cell)

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BACKGROUND

This group of Hodgkin lymphoma encompasses classical Hodgkin lymphoma and the less common nodular lymphocyte predominant Hodgkin lymphoma. 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 lympho-proliferative disorder 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. In NLPHL, the classic presentation is a male patient with a single site of non-contiguous lymphadenopathy that has been slowly enlarging for months or years. Many patients present with large solitary mass and absence of signs or symptoms of lymphoma. Nodular lymphocyte predominant Hodgkin lymphoma has a male preponderance and typically presents in middle ages (30 - 50 years). The most common sites of involvement are peripheral lymph nodes, including cervical, axillary, and inguinal lymph nodes. Mediastinal and retroperitoneal involvement is uncommon. A diagnosis of NLPHL in these locations should be made with extreme caution. Mesenteric lymph node involvement can be seen unlike CHL. Bone marrow involvement is very rare,[1] but when stage IV disease ensues, the prognosis is dismal.[2] Patients with advanced disease may display infiltration of solid organs such as spleen. Rare cases have destructive lytic lesions on the bone.

Approximately 20 % of patients present with advanced stage disease. Nodular lymphocyte predominant Hodgkin lymphoma is clinically indolent but has a higher recurrence rate than CHL; consequently, many patients die from therapy-related complications rather than from primary disease.[3] As a result, the approach to therapy has changed. Classical Hodgkin lymphoma is treated aggressively and NLPHL may be treated more conservatively, making accurate sub classification of Hodgkin lymphoma essential. On gross examination, the involved lymph node is typically grey white, lobulated and firm with a homogeneous, appearance. Microscopically, on low magnification, the lymph node architecture is partially effaced by large, often interlocking nodules. A rim of normal compressed lymph node is often present at the periphery. Unlike classical Hodgkin lymphoma, 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 been termed as popcorn cells. More recently, the preferred terminology is lymphocyte-predominant cells or LP cells.[1] 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 LP cells 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.[4] The LP cells are also 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.

Objectives

The primary objective of the study is to address the reliability of CD5 and CD3 immunopositivity on T cell rosettes surrounding LP cells and to establish the consistency of each marker as a diagnostic tool for immunohistochemistry. The purpose is to demonstrate which CD marker is more consistent with the T cell rosettes - CD5 or CD3, as it has very important diagnostic and predictive role. If CD3 predominant NLPHL is seen, drugs against CD3 molecule may be used as targeted or immunotherapy. Secondary objective of the study is to accentuate the demonstration of prototypic markers of LP cells of NLPHL such as CD20, CD45, OCT - 2 and BOB - 1, hence revisiting the significance of the above markers in immunodiagnosis.

METHODS

We retrospectively reviewed 24 cases of nodular lymphocyte predominant Hodgkin lymphoma from 2011 - 2015. Ethical clearance was obtained in two meetings conducted by the institute, one with prominent professors and heads of various oncological departments and administrative leaders of the university and district. The blocks and slides were retrieved from the archives of pathology, reviewed by three expert onco pathologists at Kidwai Memorial Institute of Oncology. 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, Thermofisher 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, ThermoFischer).

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 $P < 0.05$.

RESULTS

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 %)

Table 1. Age Distribution of Cases of NLPHL

Sl. No.	Age	Sex	CD3	CD5	CD10	BCL2	CD15	CD30	OCT - 2	BOB1
1	26	M	R	R	P	P	N	N	P	P
2	22	M	R	R	P	P	N	N	P	NEG
3	55	F	R	P	P	P	N	N	P	P
4	72	M	R	R	P	P	N	N	P	P
5	36	M	R	R	P	P	N	N	P	P
6	28	M	R	R	P	P	N	N	P	P
7	55	F	R	N	P	P	N	N	P	P
8	15	M	R	R	P	P	N	N	P	P
9	38	M	R	R	P	ND	N	FAINT P	P	P
10	50	M	R	R	N	ND	N	N	P	P
11	36	M	R	N	P	P	N	P	P	P
12	33	M	N	N	P	P	N	N	P	FOCAL P
13	29	M	R	N	P	P	N	N	P	P
14	50	M	R	N	P	P	N	N	P	P
15	25	F	R	N	P	ND	**N**	P	P	P
16	28	F	R	N	P	ND	P	P	N	P
17	28	M	R	N	P	P	N	N	P	P
18	16	M	R	N	P	P	N	N	P	P
19	29	M	R	N	P	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

Table 2. Clinical Parameters of All Cases of NLPHL Comparing with Immunohistochemical Markers

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

		CD3 IHC		
		Positive	Negative	
CD5 IHC	Positive	8 (33.3 %)	0 (0 %)	P value = 0.02
	Negative	15 (62.5 %)	1 (4.1 %)	

Table 3. Comparison of CD3 and CD5 IHC Staining in LP Cells of NLPHL

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 %)

Table 4. Comparison of All IHC Markers in LP Cells of NLPHL

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 %). 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 and 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. Eighteen cases (75 %) of NLPHL displayed CD10 positivity in the LP cells but were not considered statistically significant ($P = 0.08$). 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 of which 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

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 correspondence 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 correlation with 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 corroborative to our study. According to Hawkes EA et al.[8] CD10 shows 60 % positivity of LP cells, but was not statistically significant. In our study, we too recognised more than higher expression of CD10 (75 %), but was not statistically significant. However, several studies mention CD10 IHC is usually negative in the LP cells while BCL - 6 is a more consistent marker in these cells.

CONCLUSIONS

CD3 is a more consistent marker than CD5 in demonstrating surrounding reactive T cells in NLPHL. CD45, PAX5, CD20, BOB - 1 and OCT - 2 are consistent immunohistochemical markers of LP cells.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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