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A Clinicopathologic Comparison of Cyclin D1-Positive and Cyclin D1-Negative Lymphomas with Mantle Cell Morphology

KEYWORDS: Mantle cell lymphoma, non Hodgkin lymphoma, Cyclin D1, Immunohistochemistry

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ABSTRACT *Background:. MCL has an aggressive and incurable clinical course and frequent T(11;14)(q13;q32) translocation. The aim of this study was to investigate the value of cyclin D1 expression in B- cell non Hodgkin lymphoma with mantle cell morphology & study of clinico-pathological correlation. 171cases have been examined for lymphoma with MCL morphology from a viewpoint of cyclin D1 over expression, Using SPSS program. 138 cases (80.7%) showed positive nuclear staining for cyclin D1, while the remaining 33 (18.7%) were negative. The cyclin D1- positive group showed a higher age distribution (P .035), larger cell size (P.04), higher mitotic index (P .03) while the cyclin D 1 negative group showed significant CD 23 expression (P.003) Both cyclin D1- positive and -negative groups may represent different entities. Therefore, cyclin D1-positivity should be included as one of the standard criteria for MCL diagnosis and proper therapy.*

1. INTRODUCTION

Non Hodgkin's Lymphoma (NHL) is a broad category consisting of several distinct types of lymphoid neoplasm, 85% of which are B cell lymphomas and 15% being T cell lymphoma[1]. For establishment of therapeutic approach, clinically NHL is categorized into two major subtypes, indolent and aggressive. Indolent group includes the small lymphocytic and the follicular categories, while the aggressive group which responds well against treatment, constitutes the large cell types, the Burkitt's lymphoma and the lymphoblastic lymphomas [2]. Mantle cell lymphoma (MCL) however brings together the worst characteristics of high grade and low grade lymphomas, i.e. the course is not indolent and the disease is rarely curable[3] .The appropriate identification of lymphoma cases with mantle cell morphology as B-chronic lymphocytic leukemia/small lymphocytic lymphoma (B-CLL/SLL), low grade follicular lymphoma, multiple myeloma, splenic marginal zone lymphoma, and hairy cell leukemia, is challenging as both share many morphologic and immunophenotypic features[4] . Clinically, patients with MCL are characterized by advanced age and male predominance, presentation at advanced stages (III and IV), and frequent involvement of bone marrow (BM), peripheral blood, and other extra-nodal sites[5] . Although the international prognostic index (IPI) is an available tool for predicting lymphoma prognosis, we actually are still in need of more accurate factors for evaluation of lymphoma with mantle cell morphology[6] . MCL is mostly characterized by a monotonous proliferation of small to medium-to-large lymphocytes with scant cytoplasm and slightly irregular contoured nuclei[7] . Immunophenotypically, co-expression of cyclin D1, CD5 and pan B-cell antigens (CD19, CD20, CD22, and CD24) are characteristic of MCL[8] . So, the availability of immunohistochemical markers considerably improved the results of diagnosis in the last years[9] . Cyclin D1, CD5& CD23 have been proved by some researchers to be usually able to differentiate well between MCL & MCL like cases[10] . Also studying lymphoma with mantle cell morphology from view point of cyclin D1 over expression is essential due to the great difference in therapeutic regimens and prognosis as cyclin D1-positive MCL group, which comprises the majority of MCLs, pursues an aggressive clinical course & should be demarcated from the cyclin D1-negative group, which has a remarkably favorable prognosis[11]. Cyclin D1 belongs to the G1cyclins and plays a key role in cell cycle regulation during the G1/S transition by cooperating with cyclin-dependent kinases (CDKs)[12]. Further evidence suggests that cyclin D1 can function as an oncogene, the over-expression of which due to cytogenetic abnormality with t(11;14)(q13;q32) translocation, less commonly with t(11;22)(q13;q11) which involves a rearrangement of the BCL-1 locus in MCL, may lead to growth advantage for tumor cells by way of cell cycle progression[13] [14]. For the current study, data collected for 171 patients with lymphomas characterized by mantle cell morphology and retrospectively investigated the clinicopathologic features. The main aim was to study the different clinical & histopathologic and features of lymphoma with MCL morphology, in addition to evaluate the diagnostic role of cyclin D1, CD5 and CD23 protein expression in these lymphomas using immunohistochemical method to determine the most reliable parameters for differentiation and prediction of prognosis.

2. SUBJECTS & METHODS

2.1. SAMPLE COLLECTION

A total of 171 patients with B- NHL of mantle cell morphology were enrolled in this retrospective study. Also, patients refereed from private hospitals were included. The inclusion criteria were histo-pathologic diagnosis of B-NHL and the availability of clinical sheet details, laboratory investigations, imaging studies and paraffin-embedded tumor tissues for all cases. Excluded cases from the study were included minute biopsy specimens, tissues with extensive necrosis, cases with plasmacytoid differentiation. Routinely stained hematoxylin and eosin (H&E) slides were reviewed. Also special , Periodic Acid-Schiff, Giemsa, and silver impregnation by Gomori in some selected cases of lymphomas. Histopathologic subtyping & grading was performed based on the criteria described in the World Health Organization (WHO,2008), working formulation and Kiel classification with special attention to various histological features such as the pattern of infiltration (diffuse, vaguely nodular or mantle zone pattern), the size of cells & nuclei and the mitotic index (per 20 high-power field [HPF]).

2.2. IMMUNOHISTOCHEMISTRY

2.2.A- PROCEDURE AND ANTIBODIES

Serial 3-µm sections were cut from the paraffin block, mounted on positively charged slides and dried overnight in a 60°C oven. Sections were then de-paraffinized in xylene for 24 h

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and hydrated in a descending grades of alcohol; 100%, 90%, 85% and 70%. Antigen unmasking was performed by heat induced an epitope retrieval method by placing the slides in a plastic Coplin jar filled with citric acid buffer so that the solution covers the slides, then placing the jar in a microwave at 800Watt for 20 min (divided into 4 cycles 5 min each). The Coplin jar was then removed from the oven and allowed to cool for 15 min. Slides were placed in a humidified chamber and rinsed three times in phosphate buffer saline (PBS). Endogenous peroxidase activity was blocked by incubation of the tissue section with 3% hydrogen peroxide in water for 30 min. After washing, the tissue sections were then incubated with the primary monoclonal antibody, cyclin D1 (BLC-1 DAKO Corporation at dilution 1:50) & CD 5, monoclonal mouse anti-CD23 antibody (clone 1B12) (0.1ml supernatant) (Neo Markers, Westinghouse).

Immunohistochemistry was performed using an avidin-biotin-peroxidase system with DAB used as a chromogen and Mayer's haematoxlin applied as a light counterstain. The sections were cover-slipped by DPX mount media and examined & images were captured by the OLYMPUS CX21 Motorized System Microscope (Olympus Corporation, Tokyo, Japan). All cases were stained with CD20 to confirm B cell origin of non Hodgkin lymphomas[15] .

2.2.B- QUALITY CONTROL OF IHC

Appropriate negative controls for the immunostaining, consisting of histological sections of each case processed without the addition of primary antibody were prepared for each antigen, along with a positive control sections prepared with each IHC run then staining results were evaluated[16].

2.3. SCORING OF IHC

IHC evaluation was conducted, scored and estimated. The evaluation of immunostaining for Cyclin D1, CD5 and CD23 was scored for the percentage of immunopositive tumor cells. Cyclin D1 over expression was defined as positive in the nuclei of lymphoma cells with or without simultaneous weak staining of cytoplasm. Endothelial cells and histiocytes were used as internal positive control. Negative (-)=<10% of cells positive, Regional (+)=10-50% of cells positive, Diffuse (++) >50% of cells positive [17] . According to Watson et al [18] CD23 & CD5 positivity was identified by significant labeling of neoplastic cells (in the form of membranous reaction) in any area of the section. If positivity was only restricted to the dendritic reticulum cell network, the case was considered negative. Negative (-)=No individual lymphoid cells positive, Regional (+) =≤50% of cells positive, Diffuse (++) >50% of cells positive. CD20 positivity was identified by significant labeling of neoplastic cells in the form of membranous reaction) in any area of the section.

2.4. STATISTICAL ANALYSIS

The Statistical Package for Social Sciences (SPSS) for windows (version 12) computer program was used for statistical analysis. Comparison between positive cases was calculated by Chi square test. P values ≤0.05 and ≤0.01 were considered significant and highly significant, respectively, in all analyses.. T-test to compare mean and SD between two groups.

3. RESULTS

The association between cyclin D1 immunohistochemical expression & the clinic-pathological features of 171 studied lymphomas with mantle cell morphology are summarized in table 1. Among the 171 patients with MCL morphology, cyclin D1overexpression was detected in 138 (80.7%). The patients of both groups showed male predominance, whereas the cyclin D1-positive group showed a higher age distribution (median age, 65 and 60 years, respectively; P 5 .035). The majority of both groups presented with advanced stages (III or IV) of the disease (81.8% and 66.6%, respectively). Extra-nodal involvement was frequently recognized in both groups & BM was the most frequent site of extra-nodal involvement in both groups. Serum LDH level and performance status tended to be higher for the cyclin D1-positive group, though the difference was not statistically significant

Table (1): Association between cyclin D1 expression & clinicopathologic variables of 171 lymphomas

Parameters	Cyclin D1(+) (n=138)	Cyclin D1 (-) (n=33)	P - value
Age (y) range	32 – 82	33 – 75	
Median age	65	60	0.035
> 60	92	18	
Gender			
M	83	21	o.65
F	55	12	
Stage			
I	8	4	
II	17	7	0.42
III	38	4	
IV	75	18	
Extra-nodal involvement			
B.M	85	16	0.85
Spleen	45	9	0.75
Liver	14	5	0.82
Elevated Serum LDH > normal	45/13	12/33	0.18

Table (2): Histological & Morphological evaluation of 171 lymphomas

Parameters	Cyclin D1(+Pos) (n=138)	CyclinD1(-Neg) (n=33)	P-value
Growth pattern			
Diffuse	62	15	
Vaguly nodular	48	10	0.56
Mantle zone pattern	28	8	
Cell size			
Small	35	15	
Medium	85	18	0.04
Large	18	0	
Morpho-logical variants			
Blastoid	12	0	0.16
Pleomorphic	6	0	0.18
Mitotic Index			
Low	95	32	0.03
High	43	1	

Table (3): Phenotypic evaluation of 171 lymphomas

Immunophenotype	Cyclin D1(+) (n=138)	Cyclin D1 (-) (n=33)	P-value
CD 5 +	128/138	32/33	0.38
CD23 +	12/138	22/33	0.003

The histological & morphological evaluation of cyclin D1 positive & cyclin D 1 negative groups are summarized in table 2. The distribution of growth patterns (mantle zone, nodal, or diffuse) revealed no remarkable differences between the 2 groups. The characteristic mantle zone pattern was also seen in cyclin D1- negative patients without identification of a proliferation center. In the cyclin D1-positive group, the majority (120 patients, 86.9%) featured a monotonous population of atypical small to medium-sized lymphoid cells with irregular

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and indented nuclei, whereas pleomorphic & blastoid variants were encountered in 6 (4.3%) &12 (8.6%) respectively. Consequently, cyclin D1-positive MCL showed a larger cell size (P .04) and higher mitotic index (P .03) while cyclin D 1negative cases show no large cells & low mitotic index.

The phenotypic evaluation of both cyclin D1 positive & cyclin D1 negative groups of lymphomas is summarized in table3. Immunophenotypically, Regarding CD 5 & CD 23 they are expressed more in cyclin D1 negative group in a percentage of (96.9%) & (60.6%) respectively

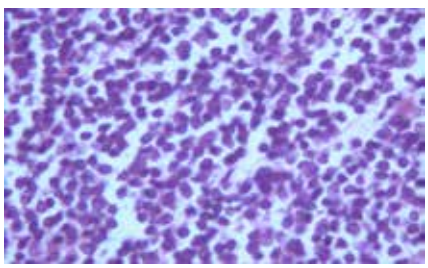

Figure (1) : Mantle cell lymphoma shows mild to moderate nuclear irregularities with clumped chromatin. (H & E X 400)

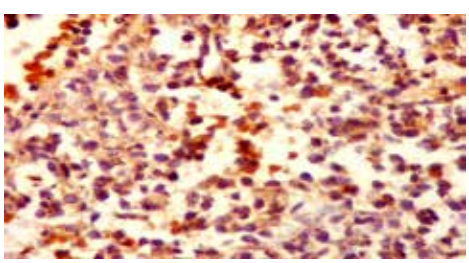

Figure (2): Mantle cell lymphoma shows positive nuclear staining for cyclin D1(immunoperoxidase staining, hematoxylin counterstain X 400)

4- DISCUSSION:

Mantle cell lymphoma is a type of B-cell NHL with distinctive morphologic and immunophenotypic features and a characteristic cytogenetic abnormality [19]. The determination of cyclin D1 status is thought to be essential for confirmation of the diagnosis of MCL , So in the current study, we examined 171 patients of lymphomas with the morphologic features of MCL because of the different clinicopathologic and significant prognostic differences between the cyclin D1- positive and -negative groups of lymphoma with mantle cell morphology. Regarding, cyclin D 1 positive lymphomas in a study performed by Roy et al 2013[20] the median age of diagnosis of cyclin D 1 positive MCL was 57 years. In the current study Cyclin D1 positive group tends to affect older individuals, the median age of diagnosis being 65 years. In a study performed by kai et al 2005[21] , The median age of cyclin D 1 negative lymphomas 61 years (range, 54-77 years) while in our study the mean age of cyclin D 1 negative group was 60 years (range, 33-75 years) diagnosis. In our study The majority of both groups presented with advanced stages (III or IV) (81.8% and 66.6%, respectively) with splenic & hepatic involvement in a percentage of 32.6% & 10.1% respectively . Also In Roy et al 2013 [20] study, there was generalized lymphadenopathy in 84.6% of cases. The spleen is involved in half of the cases and may be the only site of the disease. In a previous study carried out by Basu et al 2005 [22] , showed generalized lymphadenopathy, hepatomegaly and splenomegaly in 77%, 23% and 38.5% of cases respectively [22]. Most patients with cyclin D 1 positive lymphomas have disseminated disease , generalized lymphadenopathy & frequent bone marrow involvement. [22]. In the current study bone marrow infiltration was in a percentage of 61.6% while in Roy et al 2013 study, 81.8% had a bone marrow infiltration. From the analysis of the clinical data of the studied cases, it has been found that the most frequent clinical & laboratory finding in MCL cases after lymphadenopathy was bone marrow infiltration (85/138) & (16/33) followed by splenomegaly 32.6% (45/138) & 27.3% (9/33) then hepatomegally 10.1% (14/138) & 15.2% (5/33) in both cyclin D 1positive & cyclin D 1 negative groups respectively. On the other hand, Letestu et al 2004 [24] reported that the most frequent clinical finding in MCL cases after lymphadenopathy was splenomegaly (18/25 cases, 72%). Regarding other clinical features including sex distribution, stage, presence of B symptoms, serum lactate dehydrogenase (LDH) levels & extra-nodal sites were similar between the cyclin D1-positive and cyclin D1-negative groups which was compatible with a study of Letestu et al 2004 [24] .

By studying the histopathologic criteria, a diffuse pattern of growth was documented in 45.5% of cyclin D 1 negative lymphoma (15/33), nodular 30.3% (10/33) & mantle zone pattern 24.2% (8/33). This was lower than that reported by Nancy et al 2005 [25] . In cyclin D 1 positive group the patterns of growth were diffuse in 44.9%, (62/138) vague nodular in 34.8%,(48/138) and mantle zone in 20% (28/138) of cases. This was varied from those documented by Majlis et al1997 [26], in which the percentages of mantle zone and nodular patterns were reversed. This might be attributed to late diagnosis of Egyptian patients as they usually present at a late stage of diseases allowing the mantle zone pattern to progress into diffuse and nodular patterns that constitute the majority of the cases. Regarding the cell size, medium sized cells were dominant in both cyclin D 1positive & cyclin D 1 negative cases in a percentage of (61.6%) (85/138) & (54.5%) (18/33) respectively. Cyclin D1-positive group revealed cells of large size in (13%) of cases while these large cells were not indentified in cyclin D1 negative cases. Consequently, cyclin D1-positive cases showed a higher mitotic index than cyclin D1 negative cases & this is compatible with a study performed by Majlis et al 1997[26] .

The availability of different immunohistochemical markers considerably improved the diagnosis of mantle cell lymphoma. Cyclin D1, CD23 & CD5 have been proved to differentiate well between MCL & MCL like cases [27&28] .

The incidence of cyclin D1 protein expression with intranuclear staining in MCLs was more frequent in this study (138/171 cases, 80.7%) than that reported by Hashimoto et al. [29] (16/27 cases, 60%) , who used monoclonal antibodies on frozen sections. On the other hand, our results were less than those obtained by Singh et al [28] , who revealed that all cases of MCL showed diffuse nuclear staining with cyclin D1 polyclonal antibody on paraffin-embedded sections. This difference may be attributable to the type of fixative used, or antibodies either monoclonal or polyclonal. Also negativity in our study (33/171 cases 20%) may be lower expression than threshold level for detection by immunohistochemistery, or such cases may represent small lymphomas other than MCLs, also might due to presence of cytogenetic abnormality other than Bcl-1 rearrangement. CD 23 can be seen in as many as of these cases with focal & weak nuclear staining, in a study performed by Nancy et al 2005 [25] CD 23 was positive in 4% of cases of MCL & 62% of cases of SLL/CLL. While in our study it is expressed in (12/138) 8.7% of cases of cyclin D 1 positive group as a dot like staining pattern & 66.7% (22/33) in cyclin D1 negative group as a diffuse membranous staining pattern. This might be due to differences in used monoclone & variable cut off point used in immune scoring. Also CD23 negativity in some patients represents a shift in phenotype with loss of this antigen and consequent refractoriness to therapy [30] . So CD23 is regarded as a useful marker in differentiation in lymphoma with mantle cell morphology as it is generally positive for CLL and is generally negative for MCL [31] . In a study performed by Yasushi et al 2000 [32] most of the cyclin D1-positive and -negative patients were CD23 negative , but 14 patients were CD23positive (10 cyclin

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D1-positive and 4cyclin D1-negative). When one focused on CD23 expression, these CD23positive cyclin D1-negative patients could be B-CLL/SLL, and CD23positive cyclin D1-positive patients might be classified as cyclin D1-positive atypical CLL/SLL. However, none of the CD23+ patients showed histologic features contradictory to those described for MCL. These data suggest that CD23 is not a precise marker for the distinction of MCL and other types of low-grade B-cell lymphoma, though it is valid for a differential diagnosis of MCL and B-CLL/SLL.

In the present series, CD5 positivity is observed in both cyclin D 1 positive & cyclin D 1 negative groups in a percentage of 92.8% (128/138) & 97% (32/33) respectively. In a study performed by Kai et al 2005 [21] the expression of CD5 antigen was noted in all cyclin D 1 negative cases which is nearly compatible with the current results While in a series performed by Gujral et al 2008 [33] , there were seven out of 68 MCL cases did not express CD5. So identifying CD5 antigen expression may be useful in identifying some lymphomas, such as small cell lymphocytic lymphoma/chronic lymphocytic leukemia (LL/CLL) and the mantle cell lymphoma (ML), which are two types of lymphoproliferative diseases that progress differently, thereby requiring a correct definition.

5- Conclusion and recommendations

Therefore, it seems that Cyclin D1, CD5 and CD23 immunostaining are reliable diagnostic tools for discrimination between MCL & MCL like cases. Moreover, Cyclin D1 over expression seems to have prognostic impact in MCL. Further confirmatory studies to explain the difference between the two neoplasms in biological and clinical behavior despite common cell origin are warranted.

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