Original Article

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Mantle Cell Lymphoma and Variants: A Clinicopathological and Immunohistochemical Study

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Abstract

Introduction: Mantle cell lymphoma (MCL) is an intermediate grade lymphoma characterized by reciprocal translocation *t*(11;14)(q13;q32) which results in cyclin D1 overexpression. Several variant forms of MCL are recognized, namely, blastoid, pleomorphic, small cell, and marginal zone type. The former two are considered aggressive. The purpose of the study was to study and compare the clinicopathological and immunohistochemical (IHC) features of MCL and its variants.

Materials and Methods: All cases diagnosed as MCL in our institution over a period of 4½ years were included in this study. Histomorphology was reviewed and a panel of IHC comprising CD3, CD5, CD10, CD20, CD23, cyclin D1, Bcl6, Bcl2, Ki67, c-myc, and p53 was done on all cases.

Results: Twelve cases of MCL were identified: Four classical, six blastoid, one pleomorphic, and one small cell variant. They were grouped into non-aggressive (classical and small cell variant) and aggressive (blastoid and pleomorphic variant) groups. The aggressive group had a higher mitotic rate, Ki67 proliferative index, MCL International Prognostic Index, and poor outcome. Aberrant phenotypes such as CD5−, CD10+, and/or Bcl6+ in varying combinations were encountered in both the groups. Some cases in the aggressive group also showed strong p53 and c-myc expression.

Conclusions: Our study highlights that MCL can have different histological appearances which can lead to diagnostic confusion with various other lymphomas. Since aberrant IHC expressions are also frequent, a cautious approach using a panel of IHC markers is essential for a correct diagnosis. Blastoid and pleomorphic subtypes may strongly express p53 and c-myc and have a poor outcome.

Key words: Aberrant, Blastoid, Cyclin D1, C-myc, p53, Pleomorphic, Small cell

INTRODUCTION

Mantle cell lymphoma (MCL) is an intermediate grade B-cell lymphoma and comprises 2-10% of all non-Hodgkin lymphomas (NHL). It is characterized by reciprocal translocation *t*(11;14)(q13;q32) between the *CCND1* and the immunoglobulin heavy chain (*IgH*) genes which results in cyclin D1 overexpression. Besides the classical form, which is the most common, several morphological variants are recognized, namely, blastoid, pleomorphic, small cell and marginal zone types.[1] The former two are considered aggressive. Typical immunohistochemical (IHC) profile of MCL shows positivity for CD20, CD5, cyclin D1, and Bcl2, although variations do exist. Secondary molecular and genetic events involved in the progression of MCL are more frequently encountered in the blastoid and pleomorphic types. The aim of the present study was to study and compare the clinical, histopathological, and IHC features of MCL and its variants.

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MATERIALS AND METHODS

All cases diagnosed as MCL over a period of 4½ years (January 2011 until June 2015) in the Department of Pathology were included in this study. Information about clinical features, relevant investigations, treatment, and outcome were retrieved from the hospital records. Besides hematoxylin and eosin (H and E) sections, IHC sections were reviewed, and additional IHC staining carried out. All the cases were stained for CD3 (PS1, Biogenex), CD5 (4C7, Novocastra), CD10 (56C6, Biogenex), CD20 (L-26, Novocastra), CD23 (1B12, Novocastra), cyclin D1 (ERP-224-32, Biogenex), Bcl6 (LN22, Novocastra), Bcl2 (124, Dako), Ki67 (MM1, Novocastra), c-myc (9E10, Biogenex), and p53 (DO-7, Dako). The blastoid and pleomorphic variants were also stained for TdT (Sen28, Novocastra). All the primary antibodies were pre-diluted and ready-to-use. The detection kit used was "NovoLink polymer" from Leica Biosystems, Newcastle upon Tyne, United Kingdom.

For IHC, 4 μ paraffin sections were cut and mounted on poly-L-lysine coated slides. The sections were then deparaffinized through two changes of xylene followed by re-hydration in descending grades of ethanol, to bring sections to water. Heat-induced antigen retrieval was done in citrate buffer at pH 6.0. Subsequent steps included endogenous peroxide block, protein block, incubation with primary antibody, post-primary block and incubation with Novolink polymer. Interval washings were done with 50 mM Tris-buffered saline, pH 7.6. Final color development was achieved using 3,3'-diaminobenzidine followed by hematoxylin counter stain. Appropriate positive and negative controls were also run with each batch of staining.

Staining of Ki67, c-myc and p53 was semi-quantitatively scored by accessing percentages of positively stained nuclei in multiples of 10. For c-myc and p53, average intensity of nuclear staining was recorded as weak (+), moderate (++) or strong (+++). For the other IHC markers, results were recorded as positive if more than 10% neoplastic cells were positive.

Fluorescent *in situ* hybridization (FISH) for *t*(11;14)(q13;q32) was done in two cases (cases no. 1 and 5).

RESULTS

Twelve cases (4.8%) of MCL were identified out of a total of 252 cases diagnosed as lymphoma. Of these, four had classical morphology (case no. 1 to 4), six were blastoid (case no. 6-11) and one each was pleomorphic (case no. 12) and small cell type (case no. 5). For comparative study, classical and small cell types were grouped into non-aggressive category (Group A), while blastoid and pleomorphic types were grouped as aggressive (Group B).

The age range of patients was 45-85 years with a mean of 64 years and median of 67 years. Eleven out of 12 patients were male. Generalized lymphadenopathy (LN) (9/12), hepatomegaly (8/12), splenomegaly (4/12), bone marrow (BM) involvement (10/12), peripheral blood (PB) spill (5/12), and extra nodal involvement (ENI) (6/12) were frequent findings. ENI was found in the gastrointestinal tract (GIT) (3/12), pleural cavity (3/12), peritoneal cavity (2/12), lung (1/12), and liver (1/12). Two cases in the aggressive group and one in the non-aggressive group also had bulky confluent lymph node masses. About 10 cases had stage IV and two had stage III disease. The mean serum lactate dehydrogenase (LDH) level was 659 U/L. The clinical features and laboratory parameters are shown in Tables 1 and 2.

Table 3 shows the histopathological features of all the MCL cases. Growth pattern in the lymph nodes was mixed in 10 cases; 8 of these had diffuse and nodular

Table 1: Relevant clinical features and Ann Arbor staging of 12 mantle cell lymphoma patients[2]

Case[a]	Age/sex	LN	Hepatomegaly	Spleno megaly	Extra nodal	Peripheral blood spill	Bone marrow	Stage[b]
1	70/M	Generalized	+	+	-	-	+	IVB
2	45/M	Cervical	+	-	-	-	+	IVB
3	72M	Mediastinal	+	-	Lung	-	+	IVB
4	58/M	Generalized	+	-	GIT, PE, As	+	+	IVB
5	69/M	Cervical, tonsil, mediastinal	-	-	-	-	+	IVA
6	52/M	Generalized	+ nodules	+	Liver	+	+	IVXB
7	65/M	Generalized	+	+	PE, As	+	+	IVB
8	65/M	Generalized	-	-	GIT	+	+	IVB
9	85/M	Generalized	+	-	-	-	+	IVA
10	45/F	Generalized	-	+	GIT, PE	+	+	IVB
11	73/M	Generalized	-	-	-	-	-	IIIA
12	77/M	Generalized	+	-	-	-	-	IIIXB

As: Ascites, GIT: Gastrointestinal tract, LN: Lymphadenopathy, PE: Pleural effusion. [a]Cases 1-4 classical, case 5 small cell variant, cases 6-11 blastoid variant, case 12 pleomorphic variant. [b]Cotswold's modification of Ann Arbor Staging.

pattern, 2 had mantle zone (MZ) and nodular pattern (Figure 1a), and one purely nodular growth pattern. In one patient (case no. 3) only the BM trephine biopsy was available, which showed a nodular and interstitial pattern of infiltration. The neoplastic lymphoid cells in classical type showed centrocyte-like morphology with round indented nuclei, coarse chromatin, and inconspicuous nucleoli (Figure 2a). The blastoid variants showed lymphoblast-like morphology with slightly enlarged, rounded nuclei having fine chromatin and small nucleoli (Figure 2b). The nuclei were more enlarged and pleomorphic in the pleomorphic subtype (Figure 2c). The small cell variant showed cells with small, condensed, hyperchromatic nuclei, morphologically resembling small lymphocytic lymphoma (SLL) (Figure 2d). Other diagnostic histopathological findings included the presence of pink histiocytes and hyalinized blood vessels. Tumor cell proliferation as assessed by mean mitotic activity was 8/10 high power field (hpf) for Group A and 48/10 hpf for Group B. The median Ki67 proliferative fraction was 30% for Group A and 70% for Group B.

The IHC profile of the cases is shown in Table 4. All cases were positive for CD20, cyclin D1 and bcl2 (Figure 1b and c). Ten cases were positive for CD5 (Figure 1d). The intensity of cyclin D1 nuclear staining was heterogeneous, being weaker in the blastoid cells as compared to the centrocytic. Aberrant phenotypes such as CD5 negative (2/12), CD10 positive (2/12), Bcl6 positive (4/12), and CD3 positive (2/12) were found in various combinations in six cases. The case with small cell histology was CD5 negative and strongly positive for CD10 and bcl6 (Figure 3a-d). Aberrant expression in blastoid variants was generally of weak intensity. Two cases (cases no. 1 and 5) tested for *t*(11;14)(q13;q32) by FISH were positive, which included the small cell variant with aberrant phenotype.

Prognostic parameters and outcome of all the cases are shown in Table 5. In the non-aggressive, Group A, the mean MCL International Prognostic Index (MIPI) was 4 while in the aggressive, Group B, it was 7.5. Strong expression of c-myc (intensity 3+) was present in 2 cases

Table 2: Comparative clinical features, laboratory parameters and Ann Arbor staging of non-aggressive (Group A) and aggressive (Group B) subgroups of Mantle cell lymphoma

Group	Age (years)	Sex	Gen LN	Hepatomegaly	Splenomegaly	ENI	PB spill	BM	LDH (U/L)	Stage
A. Non-aggressive (*n*=5)	45-70 Median: 69	M=5	2	4	1	2	1	5	Mean: 510	IV=5
B. Aggressive (*n*=7)	45-85 Median: 65	M=6 F=1	7	3	3	4	4	5	Mean: 808	IV=5 III=2

BM: Bone marrow, ENI: Extra nodal involvement, Gen: Generalized, LDH: Lactate dehydrogenase, LN: Lymphadenopathy, PB: Peripheral blood

Table 3: Comparative histopathological features and Ki67 proliferative index of non-aggressive (Group A) and aggressive (Group B) subgroups of Mantle cell lymphoma

Group	Pattern	Cell morphology	Mitosis/10 Hpf	Ki67%
A. Non-aggressive (*n*=5)	MZ+N=2 D+N=2 D+I=1 (BM)	Centrocytic=4 Small cell=1	Range: 3-11 Mean: 8	Range: 10-30 Median: 30
B. Aggressive (*n*=7)	D+N=6 N=1	Blastoid=6 Pleomorphic=1	Range: 35-63 Mean: 48	Range: 60-100 Median: 70

BM: Bone marrow, D: Diffuse, Hpf: High power field, I: Interstitial, MZ: Mantle zone, N: Nodular

Table 4: Immunohistochemical profile of 12 cases of mantle cell lymphoma

Case	Type	CD20	Cyclin D1	Bcl2	CD5	CD10	CD23	Bcl6	CD3	TdT
1	Classical	+	+	+	+	-	-	-	-	ND
2	Classical	+	+	+	+	-	-	-	-	ND
3	Classical	+	+	+	+	-	-	-	-	ND
4	Classical	+	+	+	+	-	-	+w	-	ND
5	Small cell	+	+	+	-	+	-	+	-	ND
6	Blastoid	+	+	+	-	-	-	-	-	-
7	Blastoid	+	+	+	+	+w	-	+w	-	-
8	Blastoid	+	+	+	+	-	-	+w	+w	-
9	Blastoid	+	+	+	+	-	-	-	+w	-
10	Blastoid	+	+	+	+	-	-	-	-	-
11	Blastoid	+	+	+	+	-	-	-	-	-
12	Pleomorphic	+	+	+	+w	-	-	-	-	-

ND: Not done, w: Weak

Table 5: Prognostic parameters and outcome of 12 patients with mantle cell lymphoma

Case	Type	MIPI[a]	c-myc[b]	p53[b]	Outcome
1	Classical	3 (low risk)	70% (++)	70% (++)	Relapse at 2 years and 3 months
2	Classical	4 (Int. risk)	ND	ND	No follow-up
3	Classical	7 (high risk)	0%	10% (+)	No follow-up
4	Classical	3 (low risk)	80% (++)	30% (+)	No follow-up
5	Small cell	3 (low risk)	60% (++)	60% (+)	In remission at 3 years
6	Blastoid	ND	50% (++)	40% (+)	Progressive disease at 3 months of follow-up
7	Blastoid	11 (high risk)	60% (++)	90% (+++)	Expired before treatment
8	Blastoid	6 (high risk)	80% (+++)	40% (++)	Expired before treatment
9	Blastoid	3 (low risk)	0%	10% (+)	In remission at 1 year
10	Blastoid	8 (high risk)	30% (+++)	40% (++)	Relapse at 1 year; progressive disease after 6 months
11	Blastoid	8 (high risk)	40% (++)	40% (+)	Expired after 6 months
12	Pleomorphic	9 (high risk)	10% (+)	70% (+++)	On induction therapy since 2 months

ND: Not done, Int: Intermediate, MIPI: Mantle cell lymphoma International Prognostic index. [a]MIPI 0-3 Low risk, 4-5 Intermediate risk, 6-11 high risk. [b]+weak, ++ moderate, +++ strong positive intensity of staining

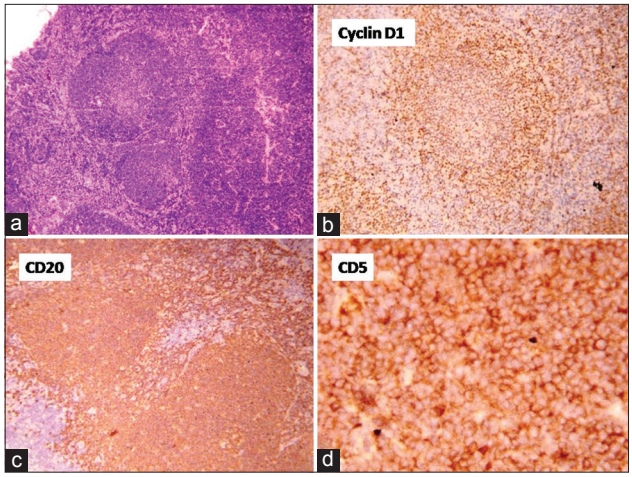

Figure 1: (a) Mantle zone and nodular pattern of growth (H and E, ×40). (b-d) Immunohistochemistry showing cyclin D1, CD20, and CD5 positivity in classical mantle cell lymphoma. 3,3'-diaminobenzidine chromogen

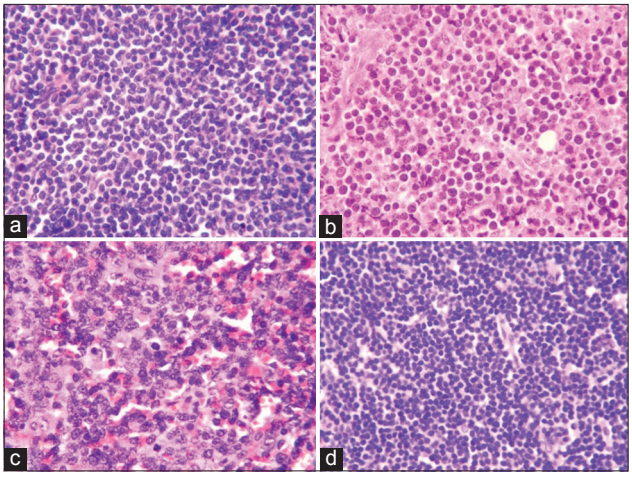

Figure 2: Histological types of mantle cell lymphoma. (a) Classical centrocyte-like (b) Blastoid (c) Pleomorphic (d) Small cell chronic lymphocytic leukemia/small lymphocytic lymphoma-like (H and E, ×400)

of blastoid MCL while strong expression of p53 (intensity 3+) was found in one case each of blastoid and one pleomorphic MCL (Figure 3e and f). None of the Group A cases showed strong intensity of c-myc or p53 staining. Weak to moderate intensity of staining was found in all the subtypes. Three patients of blastoid MCL expired, two had progressive disease, and one is in remission. One patient of pleomorphic type was on induction therapy.

DISCUSSION

Epidemiology

MCL is an intermediate grade B-cell lymphoma and comprises 2-10% of all NHL.[1-4] In the data published from two large Indian studies, MCL constituted 2.1% and 3.4% of all NHL as compared to 4.8% in our institutional series.[5,6] MCL with classical histology is the most common and comprises 80-90% of cases. The remaining 10-20% of cases are variants of MCL and include blastoid, pleomorphic, small cell and marginal zone subtypes.[1,7-9]

MCL is common in middle-aged or elderly individuals with a median age of 60 years.[1,7,10] Our patients had a mean age of 64 years and median of 67 years. There is a striking male predilection with the male to female ratio in different studies ranging between 2.3-4.5:1.[3,6,7,10,11] This strong gender preference was also reflected in our study.

Clinical Features

Most patients of MCL, irrespective of their histological subtype, present with advanced stage disease (stage III or IV), with lymph nodes being the most common site of involvement. ENI is frequent, and commonly includes the spleen, BM, PB, GIT, Waldeyer's ring and pleura.[1,5-7] All our cases had LN and advanced stage disease (either stage III or IV) at presentation. Generalized LN, splenomegaly, and PB spill were more common in the aggressive group. In a study of 187 patients of MCL, a higher percentage of ENI (66%), PB spill (48%) and BM infiltration (82%) was found in the blastoid subgroup.[8] Among the six cases of blastoid MCL in the present study, four cases each had ENI

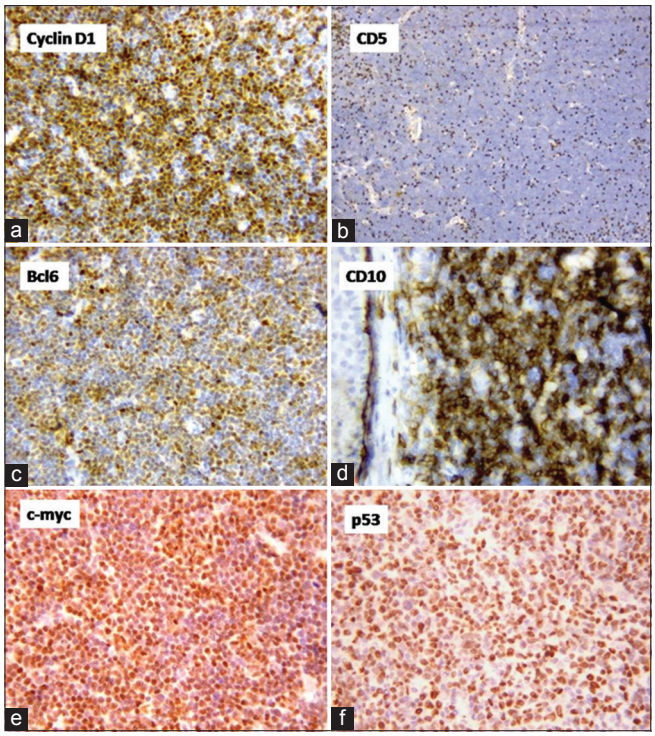

Figure 3: (a-d) Small cell variant showing aberrant CD5–, Bcl6+ and CD10+ phenotype with cyclin D1 expression (e) Blastoid mantle cell lymphoma (MCL) with strong c-myc expression (f) Pleomorphic MCL with strong p53 expression. 3,3'-diaminobenzidine chromogen

and PB spill, and five had BM infiltration. GIT and pleural cavity were the other commonly involved extra nodal sites.

Histopathology

Histopathology of nodal MCL shows complete or partial effacement of architecture with a diffuse, nodular, MZ, or a mixed pattern of growth. Out of these, mixed (nodular and diffuse) and diffuse patterns are the most common.[1,5,6,11] Most cases in our study showed a mixed nodular and diffuse pattern of involvement. There was no apparent difference in the pattern of involvement between aggressive and non-aggressive groups. However, areas with MZ pattern were seen only in the classical category.

The lymphoid cells of classical MCL are small to intermediate in size and have centrocyte-like morphology. Mitotic activity is variable but generally low. In the blastoid variant, the nuclei are larger with round to irregular contours, fine chromatin, and inconspicuous nucleoli. The pleomorphic subtype shows lymphoid cells with greater variation in size and shape, coarser chromatin, and conspicuous nucleoli at least in some cells. Blastoid and pleomorphic phenotypes may represent a continuum with some cases showing both the morphologies in different areas of the same lymph node. At times, it may be difficult to segregate blastoid from pleomorphic cells because of intermediate morphology.[12] One case categorized as pleomorphic type in our series had areas showing both blastoid and pleomorphic morphology. Blastoid and pleomorphic subtypes show high mitotic activity (>20-30/10 hpf) often with tingible-body macrophages. The small cell variant is an uncommon and indolent subtype of MCL. It is characterized by smaller lymphoid cells with condensed nuclear chromatin resembling cells of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Mitotic activity and Ki67 proliferative index is lower than classical subtype.[13] The marginal zone-like variant shows foci of cells with abundant pale cytoplasm or monocytoid B-cells mimicking marginal zone lymphoma. Hyalinized small vessels and pink histiocytes are other important diagnostic findings in MCL.[1] BM infiltration by MCL is usually diffuse or nodular, and may occasionally show paratrabecular or intrasinusoidal growth pattern.[12]

Since MCL can show morphological diversity, several other lymphomas enter into the differential diagnosis such as CLL/SLL, follicular lymphoma, marginal zone lymphoma, lymphoblastic lymphoma and diffuse large B-cell lymphoma. Hence, IHC is essential for an accurate diagnosis.

Immunohistochemistry

Typical IHC profile of MCL shows positivity for CD20, CD5, cyclin D1, and Bcl2 with negativity for CD10, CD23, and BCL6. Aberrant phenotypes are not uncommon and can be encountered in cases with both classical and blastoid morphology, the frequency being higher in the latter.[1] These variations include CD5−, CD23+, CD10+, Bcl6+, and cyclin D1− in isolation or in various combinations.[14,15] In our series, six out of 12 cases showed aberrant IHC. The case with small cell morphology, not only showed aberrant loss of CD5 but was also positive for CD10 and Bcl6, bringing in a differential diagnosis of follicular lymphoma. However, positivity for cyclin D1, established the diagnosis, which was later also confirmed by FISH for *t*(11;14)(q13;q32). The aggressive group in our series also showed greater phenotypic aberrancy. A small number of morphologically typical MCL cases are cyclin D1 negative. These can be identified using SOX11, a novel diagnostic marker for MCL, having more than 90% sensitivity.[16]

Our results support the fact that immunophenotypic variations are common in MCL, and recognizing this variability is important for accurate sub-classification of B-cell lymphomas. In cases with inconclusive IHC, molecular testing becomes essential for confirmation of diagnosis.

Molecular Genetics

The characteristic reciprocal translocation *t*(11;14)(q13;q32) is the initial molecular event in MCL and

can be identified in up to 99% of cases by FISH.[17] The translocation results in constitutive over-expression of cyclin D1 which is a cell cycle regulator and drives the cell beyond the G1/S-phase check point, leading to B-cell proliferation. Subsequently, several secondary genetic events in the form of gains and losses occur causing disease progression. Besides cell cycle deregulation, other molecular mechanisms implicated in pathogenesis are alterations in DNA damage response pathway and activation of cell survival pathways. Different studies have identified alteration in the *ATM, TP53, c-myc,* and *Bcl6* genes in association with disease progression.[9,18-21]

Since *c-myc* and *p53* gene alterations have been implicated with aggressiveness and poor outcomes in patients with MCL, we studied their protein expression by IHC. Correlation between *c-myc* and *p53* molecular alterations and protein expression by IHC in lymphomas has been documented in some studies.[22-25] Strong intensity of c-myc expression (3+) was found in two cases of blastoid MCL. Similarly, strong expression (3+) of p53 was observed in one case of blastoid and one case of pleomorphic MCL. None of the cases in the non-aggressive group showed strong expression of these two markers. The percentage of tumor cells expressing these markers were, however, very variable.

Treatment and Prognosis

Based on the MIPI score, treatment options for MCL patients include observation alone, combination chemotherapy with R-CHOP or R-Bendamustine and BM stem cell transplant, either autologous or allogenic.[26] At the time of relapse, agents directed at activated pathways in MCL cells such as bortezomib (nuclear factor kappa B inhibitor) or lenalidomide (anti-angiogenesis) can be used.[26]

Clinically, MCL displays an aggressive course, with a continuous relapse pattern and a median survival of only 3-7 years. The main biological parameters related to an unfavorable prognosis in MCL are high MIPI score, blastoid and pleomorphic morphology, and an increased level of proliferation.[9,18,21,27,28]

Clinically, MIPI is the prognostic model most often used and incorporates Eastern Cooperative Oncology Group performance status, age, leukocyte count, and LDH levels. In a large study on data from 455 MCL patients, the median overall survival directly correlated with MIPI.[27] In our series, the blastoid and pleomorphic subtypes had a higher mean MIPI score, a higher mitotic and Ki67 proliferative index, and poorer outcome as compared to the classical and small cell subtypes. The small cell variant generally has a lower proliferative fraction and an indolent clinical course.[12] One patient of small cell variant in our series who had an MIPI of 3 (low risk), mitotic index of 3/10 hpf and Ki67 proliferative fraction of 30%, is in remission at 3 years.

CONCLUSIONS

Because of varying cytoarchitectural and morphological appearances MCL can be confused with various other lymphomas. Though cyclin D1 is a reliable marker for all forms of MCL, aberrant IHC expressions are also common. Hence, a cautious approach with a panel of IHC markers is essentially recommended for an accurate diagnosis of MCL. In cases with inconclusive IHC, molecular testing becomes necessary for confirmation of diagnosis. Strong p53 and c-myc expression by IHC along with higher Ki67 proliferative indices may be seen in the aggressive subtypes and might contribute toward poor prognosis.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

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REFERENCES

1. Swerdlow SH, Campo E, Seto M, Muller-Hermelink HK. Mantle cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al.*, editors. WHO Classification of Tumours of Haemopoietic and Lymphoid Tissue. 4th ed. Lyon: International Agency for Research on Cancer (IARC); 2008. p. 229-32.
2. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, *et al.* Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7:1630-6.
3. Smedby KE, Hjalgrim H. Epidemiology and etiology of mantle cell lymphoma and other non-Hodgkin lymphoma subtypes. Semin Cancer Biol 2011;21:293-8.
4. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's lymphoma classification project. Blood 1997;89:3909-18.
5. Gujral S, Agarwal A, Gota V, Nair R, Gupta S, Pai SK, *et al.* A clinicopathologic study of mantle cell lymphoma in a single center study in India. Indian J Pathol Microbiol 2008;51:315-22.
6. Naresh KN, Srinivas V, Soman CS. Distribution of various subtypes of non-Hodgkin's lymphoma in India: A study of 2773 lymphomas using R.E.A.L. and WHO Classifications. Ann Oncol 2000;11:63-7.
7. Bosch F, López-Guillermo A, Campo E, Ribera JM, Conde E, Piris MA, *et al.* Mantle cell lymphoma: Presenting features, response to therapy, and prognostic factors. Cancer 1998;82:567-75.
8. Bernard M, Gressin R, Lefrère F, Drénou B, Branger B, Caulet-Maugendre S, *et al.* Blastic variant of mantle cell lymphoma: A rare but highly aggressive subtype. Leukemia 2001;15:1785-91.
9. Jares P, Colomer D, Campo E. Molecular pathogenesis of mantle cell

lymphoma. J Clin Invest 2012;122:3416-23.
10. Argatoff LH, Connors JM, Klasa RJ, Horsman DE, Gascoyne RD. Mantle cell lymphoma: A clinicopathologic study of 80 cases. Blood 1997;89:2067-78.
11. Roy A, Kar R, Basu D. Nodal mantle cell lymphoma: A descriptive study from a tertiary care center in South India. Indian J Pathol Microbiol 2013;56:94-7.
12. Klapper W. Histopathology of mantle cell lymphoma. Semin Hematol 2011;48:148-54.
13. Kimura Y, Sato K, Imamura Y, Arakawa F, Kiyasu J, Takeuchi M, *et al.* Small cell variant of mantle cell lymphoma is an indolent lymphoma characterized by bone marrow involvement, splenomegaly, and a low Ki-67 index. Cancer Sci 2011;102:1734-41.
14. Gao J, Peterson L, Nelson B, Goolsby C, Chen YH. Immunophenotypic variations in mantle cell lymphoma. Am J Clin Pathol 2009;132:699-706.
15. Zanetto U, Dong H, Huang Y, Zhang K, Narbaitz M, Sapia S, *et al.* Mantle cell lymphoma with aberrant expression of CD10. Histopathology 2008;53:20-9.
16. Mozos A, Royo C, Hartmann E, De Jong D, Baró C, Valera A, *et al.* SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. Haematologica 2009;94:1555-62.
17. Dreyling M, Kluin-Nelemans HC, Beà S, Klapper W, Vogt N, Delfau-Larue MH, *et al.* Update on the molecular pathogenesis and clinical treatment of mantle cell lymphoma: Report of the 11th annual conference of the European mantle cell lymphoma network. Leuk Lymphoma 2013;54:699-707.
18. Beà S, Ribas M, Hernández JM, Bosch F, Pinyol M, Hernández L, *et al.* Increased number of chromosomal imbalances and high-level DNA amplifications in mantle cell lymphoma are associated with blastoid variants. Blood 1999;93:4365-74.
19. Setoodeh R, Schwartz S, Papenhausen P, Zhang L, Sagatys EM, Moscinski LC, *et al.* Double-hit mantle cell lymphoma with MYC gene rearrangement or amplification: A report of four cases and review of the literature. Int J Clin Exp Pathol 2013;6:155-67.
20. Hao S, Sanger W, Onciu M, Lai R, Schlette EJ, Medeiros LJ. Mantle cell lymphoma with 8q24 chromosomal abnormalities: A report of 5 cases with blastoid features. Mod Pathol 2002;15:1266-72.
21. Royo C, Salaverria I, Hartmann EM, Rosenwald A, Campo E, Beà S. The complex landscape of genetic alterations in mantle cell lymphoma. Semin Cancer Biol 2011;21:322-34.
22. Valera A, López-Guillermo A, Cardesa-Salzmann T, Climent F, González-Barca E, Mercadal S, *et al.* MYC protein expression and genetic alterations have prognostic impact in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Haematologica 2013;98:1554-62.
23. Tapia G, Lopez R, Muñoz-Mármol AM, Mate JL, Sanz C, Marginet R, *et al.* Immunohistochemical detection of MYC protein correlates with MYC gene status in aggressive B cell lymphomas. Histopathology 2011;59:672-8.
24. Hernandez L, Fest T, Cazorla M, Teruya-Feldstein J, Bosch F, Peinado MA, *et al.* p53 gene mutations and protein overexpression are associated with aggressive variants of mantle cell lymphomas. Blood 1996;87:3351-9.
25. Zettl A, Meister S, Katzenberger T, Kalla J, Ott MM, Müller-Hermelink HK, *et al.* Immunohistochemical analysis of B-cell lymphoma using tissue microarrays identifies particular phenotypic profiles of B-cell lymphomas. Histopathology 2003;43:209-19.
26. Vose JM. Mantle cell lymphoma: 2013 Update on diagnosis, risk-stratification, and clinical management. Am J Hematol 2013;88:1082-8.
27. Hoster E, Dreyling M, Klapper W, Gisselbrecht C, van Hoof A, Kluin-Nelemans HC, *et al.* A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 2008;111:558-65.
28. Determann O, Hoster E, Ott G, Wolfram Bernd H, Loddenkemper C, Leo Hansmann M, *et al.* Ki-67 predicts outcome in advanced-stage mantle cell lymphoma patients treated with anti-CD20 immunochemotherapy: Results from randomized trials of the European MCL network and the German low grade lymphoma study group. Blood 2008;111:2385-7.

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