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A clinicopathological study of mantle cell lymphoma – single center study in northeastern India

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Abstract

Background: Mantle cell lymphoma (MCL) is a rare yet aggressive non-Hodgkin's Lymphoma (NHL). It arises from a subset of naïve pre germinal center B cells or the mantle zone of secondary follicles eliciting a pathognomonic chromosomal translocation t (11; 14).

Objective: To study the clinic pathological and immunohistochemical features in various forms of MCL.

Methods: This study comprises of nine cases of MCL diagnosed over a period of five years. It accounts for 7.69% of all non-Hodgkin's lymphoma diagnosed in our center. All nodal and extranidal cases were included in the study with exclusion of previously diagnosed or treatment-initiated cases.

Results: The mean age of presentation was 55.2 years and the male to female ratio was 1.25:1 showing slight male preponderance. Few of the cases presented with hepatosplenomegaly. Two cases showed nodular pattern on biopsy while remaining seven cases were of diffuse pattern. A single case was recorded with blastic cytomorphology showing significantly high mitotic rate. Immunophenotyping shows CD20, CD5 and Cyclin D1 positivity and were negative for CD23 and CD10.

Conclusion: In our experience, MCL patients from northeaster India had higher incidence of B symptoms and comparatively high overall incidence with respect to other studies conducted in India. Regardless of the various close differentials, histomorphology remains the mainstay in its diagnosis at resource limited areas. This study provides an insight into the need for accurate histomorpho logical diagnosis of MCL in a developing nation.

Keywords: Mantle cell lymphoma, Cyclin D1, non-Hodgkin's Lymphoma, Histopathology

Introduction

Mantle cell lymphoma (MCL) is a rare and unique type of mature B-cell lymphoid malignancy with a heterogeneous architecture and generally aggressive clinical course.1 It originates from a subset of naïve pregerminal center cell or the mantle zone of secondary

follicles.2 Mantle cell lymphoma accounts for 2-10% of all non-Hodgkin's lymphomas (NHL).2,3 It occurs in middle aged to older individuals with a male predominance (3:1). The median age of diagnosis is around 71 years.4 Lymph nodes are the most commonly involved sites. The extranodal sites frequently involved are the gastro- intestinal tract, waldeyers ring, lungs and pleura. Uncommon with distinctive presentation is with multiple intestinal polyp (multiple lymphomatous polyposis), kidney and CNS involvement at the time of relapse. Most patients present with stage III or IV disease with lymphadenopathy, hepatosplenomegaly and bone marrow involvement. Mantle cell lymphoma expresses CD20 and CD5 while CD10 and CD23 is negative with the pathologic hallmark t (11; 14) (q13, q32) translocation that leads to an overexpression of Cyclin D1 (CCND1). MCL is also positive for SOX 11 a neural transcription factor. Nevertheless, the presence of SOX 11 is believed to be more useful in diagnosing Cyclin D1 negative MCL.5 The histomorphology of Mantle cell lymphoma overlaps with the features of low-grade lymphoma, including follicular lymphoma, small lymphocytic lymphoma and marginal zone lymphoma. Hence, its accurate diagnosis by studying the clinicopathological features in combination with a meticulous immunohistochemistry is of utmost importance.

Materials and methods

This study comprises of nine cases of MCL diagnosed over a period of five years (February 2016 to November 2021) in our institute. All cases of nodal and extra nodal sites were included in the study. The cases in which treatment has been started or previously diagnosed were excluded from the study. Detailed clinical information was recorded in a predesigned proforma including the age and sex of the patients, duration of illness, site of biopsy, distribution of the disease, presence or absence of B symptoms and peripheral blood findings. All the cases were diagnosed by biopsy followed by Immunohistochemistry. This study was conducted after approval by the institutional ethics committee.

Diagnostic criteria

Only newly diagnosed cases of MCL were selected. Three out of nine cases were extra nodal in origin. Primary diagnoses based on Hematoxylin and Eosin (H and E) sections were done following strict histologic and recently updated criteria (WHO classification of 2022). The following histomorphology features were evaluated:

- Monomorphic lymphoid proliferation
- Cell Characteristics
- Pattern:
- Vaguely nodular
- Diffuse
- Mantle Zone
- Rarely Follicular Growth Pattern
- Morphologic variants
- Hyalinized vessels
- Pink histiocytes
- Number of mitotic figures per 10 random high-power field (hpf)
- Non Neoplastic Plasma cells seen

Subsequently, all nodal and extranodal samples were immunophenotyped by immunohistochemical staining for CD20, CD5, CD10, CD3, CD23, cyclin D1, and Ki-67. Ki67 used to see the aggressiveness and assessed by counting Ki-67-positive neoplastic cells in ten random high-power fields (HPF, × 400) (five HPF in small biopsies).6 Tumor cell with classical histomorphological features in a CD20 positive NHL showing expression of

Cyclin D1 and/or CD5 while negative for CD23 and CD10 were a requirement for diagnosis of MCL.

Results

In our study, MCL consisted of 7.69% (9 out of 117) of all malignant lymphoma diagnosed between February 2016 to November 2021. The clinic hematological characteristics of the nine cases were summarized in the Table 1. The mean age of presentation was 55.2 years. There was a slight male preponderance (M: F= 1.25:1).66.67% patient presented with nodal and 33.33% presented with extra nodal (nasopharyngeal mass, tonsillar growth and oropharyngeal growth) involvement. In the present study, three out of the nine cases show the presence of splenomegaly (33.33%) and two out of the nine cases of MCL shows hepatomegaly (22.22%). Most patients were noted to have systemic B symptoms like fever, night sweats, loss of appetite and weight (66.67% of cases). None of the cases were seen to have involved the peripheral blood.

Case No	Age(years)	Sex	Nodal/extranodal	Hepatomegaly	Splenomegaly	B symptoms	PS
1	17	M	N	-	-	+	-
2	40	F	N	-	13 cm	+	-
3	69	M	EN	-	-	+	-
4	58	F	EN	-	-	-	-
5	60	F	N	-	-	+	-
6	45	M	N	-	-	+	-
7	70	F	N	5 cm	9 cm	-	-
8	72	M	N	4 cm	14 cm	-	-
9	66	M	EN	-	-	+	-

Table 1: Clinic hematological profile of nine patients of MCL.

Abbreviations: M-Male, F-Female, N-Nodal, EN-Extra nodal, PS-Peripheral blood smear

Histological findings

Gross: - The group of the lymph nodes and in the case of the extra nodal mantle cell lymphoma sites were noted. The size and number of lymph nodes and whether it was discrete or matted were mentioned. Small lymph nodes were submitted in toto for processing.

Microscopy: At low power, the lymph nodes showed complete effacement of the lymph nodal architecture. They were composed of monomorphic lymphoid proliferation with a vaguely nodular, diffuse and rarely follicular pattern. Two of the cases had a nodular pattern and rest seven cases were of diffuse pattern. Follicular pattern was noted within some of the diffuse patterns. At higher power, The lymphocytic cells were small with slightly irregular nuclear contours. The nuclei have dispersed chromatin with inconspicuous nucleoli (Figure1a) Some of the cases had a plastic morphology comprising of small to intermediate sized tumor cells with finely dispersed nuclear chromatin and small nucleoli hence they were stained with Ki67 to evaluate the proliferative fraction. Mitotic count ranged from as low as 05/10 HPF to to as high as 58/10 HPF. Plastic MCL showed increased mitotic counts and a diffuse pattern. Hyalinized small vessels were present in most of the cases (Figure1b). Scattered histiocytes with eosinophillic cytoplasm was also noted. Plasma cells are seen at places but only one case showed plenty of plasma cells thus signifying plasma cell differentiation. The histopathological findings in these patients of MCL are summarized in Table 2.

Case no	Pattern	Insitu lesion	Pink histiocytes	Hyalinised vessels	Plasma cells	Mitosis /10 hpf	Morphological type
1	Diffuse	-	-	+	_	12	Lymphocytic
2	Diffuse	-	+	+	+	15	Lymphocytic
3	Diffuse	-	+	+	+++	08	Lymphocytic
4	Diffuse	-	+	+	_	32	Blastic
5	Diffuse	-	+	+	_	16	Lymphocytic
6	Diffuse	-	-	+	_	10	Lymphocytic
7	Nodular	-	+	+	_	14	Lymphocytic
8	Diffuse	-	+	+	+	58	Blastic
9	Nodular	-	+	+	-	05	Lymphocytic

Table 2: Histopathological findings in nine patients of MCL

Abbreviations: hpf-High power field

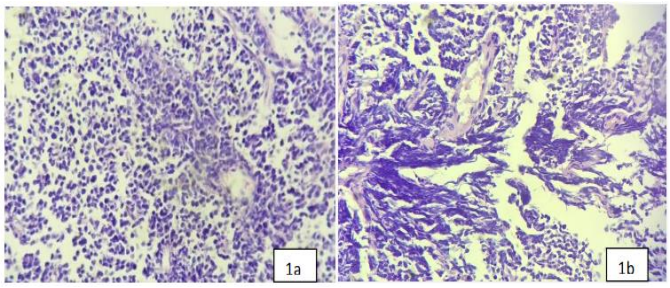

Figure 1: Lymph node biopsy showing(a) diffuse pattern of infiltration by monomorphic small lymphoid cells with scanty cytoplasm, irregular cleaved nuclei and occasional scattered pinkhistiocytes (b) hyalinised blood vessel (H and E, ×400)

Immunohistochemical findings:

MCL is known to have variable architectural and cytological patterns and each subtype has many look-alikes. Among the seven cases showing diffuse pattern one had a differential of SLL and another as undifferentiated carcinoma. Cytokeratin was done for confirmation that turned out to be negative (Figure 2a). In two cases with nodular pattern one had a differential of SLL. Final diagnosis was done by IHC in all cases. CD 20 was positive in all the nine cases of MCL with CD5 and Cyclin D1 expression. (Figure 2b-d) CD 23 and CD 10 were negative for all cases (Figure 2e and f) except one extra nodal tumour from naspharynx showing weakly positive CD23(Figure 2). Ki67 noted staining in more than 30% of the cells in six out of nine cases. This depicts a high proliferation rate in the tumours. Table 3 shows the Immunohistochemical profile of nine patients of MCL.

Case no	Morphological type of MCL	CD 20	CD 5	CD 10	CD 23	Cyclin D1	Ki67(% of cells stained)
1	Lymphocytic	+	+	-	-	+	≥ 30
2	Lymphocytic	+	+	-	-	+	≥ 30
3	Lymphocytic	+	+	-	Weakly positive	+	≥ 30
4	Blastic	+	+	-	-	+	
5	Lymphocytic	+	+	-	-	+	≥ 30
6	Lymphocytic	+	+	-	-	+	≥ 30
7	Lymphocytic	+	+	-	-	+	
8	Blastic	+	+	-	-	+	≥ 30
9	Lymphocytic	+	+	-	-	+	

Table 3: Immunohistochemical profile of nine patients of MCL

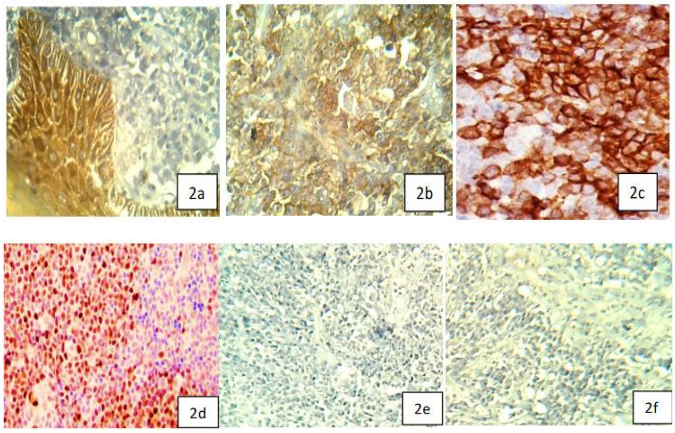

Figure 2: Immunohistochemical panel showing (a) negative cytokeratin (CK)in one case with a differential of undifferentiated carcinoma. Positive expression of (b) CD20 membranous, (c) CD5 cytoplasmic and membranous (d)cyclin D1 nuclear and negative expression of (e) CD23 and (f) CD10 (immunohistochemistry, ×400) Treatment and outcome Follow up was available in four out of nine cases while two patients expired within a year. The rest were treated with cyclophosphamide, hydroxyurea, daunorubicin, oncovin, prednisolone, cyclo phosphamide, vincristine, prednisolone, cyclophosphamide, etoposide, oncovin,

prednisolone and bendamustine, with or without rituximab, depending upon the feasibility.

Discussion:

Mantle cell lymphoma (MCL) is considered to be an aggressive form of NHL with a reported median survival of only three to four years.7 Overexpression of Cyclin D1 is a key event in the pathogenesis of MCL, and it is largely associated with a translocation t [11;14] (q13;q32).1In western countries, MCL comprises about 3% to 10% of adult-onset NHL, and its incidence is rising, with an estimated 3320 cases diagnosed in 2016.8,9 In India, it is observed that 6% of all newly diagnosed NHL are MCL with a median age of diagnosis around 57 years.10Another study by Marcucci M et al noted that MCL affects male individuals in the sixth and seventh decades of life.11 In the present study which was conducted for a period of five years, the incidence of Mantle cell lymphoma was 7.69% and the mean age was noted to be 55.2 years which is very similar to the above mentioned studies. Mantle cell lymphoma is more common in males and usually affects older people.12 Out of the nine cases of mantle cell lymphoma in our study five were males and four were females so the male: female ratio was 1.25: 1 showing a slight male preponderance. In our study seven cases were above 45 yrs of age, and the other two cases were 17 and 40 respectively. The eldest and the youngest cases were 72 years and 17 years.

It has been noted that MCL in the oral cavity has been reported in few cases, and most of them include the involvement of the palate and the tongue.11 In the present study most of the cases were from cervical nodes and inguinal nodes. Only three cases were recorded to be extranodal arising from nasopharynx, tonsil and oropharynx. According to a study conducted by Radhakrishnan V et al about 70-80% of MCL present with aggressive lymphadenopathy or extranodal disease whereas few cases are seen as asymptomatic nodal/extranodal disease.4 Another study added that the clinical course of MCL can be smouldering nodal/ extranodal or asymptomatic non blastoid leukemic non nodal.13,14,15Most of the patients present with abdominal distension due to hepatosplenomegaly.4 Extranodal involvement of GI tract , lungs and or central nervous system and orbit are seen. An uncommon, yet distinctive presentation is the occurrence of multiple lymphomatous polyposis.16 In our study two cases (22.22%) showed hepatomegaly of 4cm and 5cm and three cases (33.33%) showed splenomegaly of 9cm, 13cm and 14cm. We did not encounter any extranodal GI tract, lung or 9 CNS involvement. According to, Radhakrishnan VS et al B symptoms like unintentional weight loss, drenching night sweats, and fever are seen in about 40% of the patients.4 In the present study there was presence of B symptoms in 66.67% of the cases which is slightly more. Though leukaemia is seen in many studies this study shows absence of involvement in peripheral blood.

MCL presents as a spectrum of morphological findings with classical (lymphocytic) tumour showing small sized lymphocytes, irregular nuclei and inconspicuous nucleoli. However, on the other end blastoid and pleomorphic variants have high proliferation rate, intermediate sized lymphocytes and few small nucleoli.17 Rare variants are small cell and marzinal zone like MCL.

In our study only lymphocytic and blastic variants were noted. Two out of nine cases were blastic. The mitotic count ranged from 5/10 hpf to 58/10hpf. Mitosis was recorded to be higher in the cases with blastic morphology. A study conducted by Roy A et al recorded that, Pink histiocytes and hyalinised blood vessels are commonly seen and plays an important role in the diagnosis.2 Seven cases in the present study showed presence of pink scattered histiocytes and almost all had hyalinised vessels which are similar to other studies. Abundant plasma cells suggesting plasma cell differentiation was seen in one case although there were plasma cells in few other cases.

Immunophenotypic aberrations in MCL have been described in numerous studies.18 This is due to origin from the germinal center and/or post germinal center B lymphocytes through the somatic hypermutation of the immunoglobulin heavy-chain variable region (igvh), especially IGHV3-21, IGHV3-23, IGHV4-34, and IGHV4-59.19 Generally, the neoplastic cells are positive for CD 5 and CD 20 and negative for CD 10 and CD 23.2 Our study shows CD 5 and CD 20 positive in all cases and CD 10, CD 23 negative in all cases except one with weak positivity. According to Saksena A et al, a subset of MCL cases can be CD23+.The study also added that there were no notable difference in the frequency of morphologic subtypes between CD23+ and CD23-negative MCL.20 Enhanced Cyclin D1 staining in MCL is largely attributed to t(11;14) and the location of the CCND1 allele in the cytoplasm, nucleoli in transcription factor rich areas in the perinucleolar area, and truncated mrna of Cyclin D1.This is associated with poor prognosis.21,22,23 The overexpression of Cyclin D1 is found to be highly characteristic of MCL. In the present study, it was observed that 100% (9) of the cases were 10 positive for Cyclin D1.This is similar to the study conducted by Roy A et al.2 Six out of nine cases (66.67) had a high proliferative index (>30 Ki-67-positive neoplastic cells in 10 random high-power fields (HPF, × 400) (5 HPF in small biopsies)

In the present study, histomorphologically two cases out of nine had a differential of small lyphocytic lymphoma and one case had a differential diagnosis of undifferentiated carcinoma. This was an extranodal growth in the oral cavity. IHC staining for Cytokeratin was done that turned out to be negative.It was positive for CD20, CD 5 and Cyclin D1 and negative for CD10 and CD 23.

To conclude, Mantle cell lymphoma (MCL) is considered to be an aggressive form of NHL with challenges in its management due to its resistant and relapsing pattern.4 Some close differentials based on morphology has been documented like follicular lymphoma, small lymphocytic lymphoma, diffuse large B cell lymphoma and diffuse variant of follicular center cell lymphoma. IHC plays an important role in its diagnosis.3 Despite improvements in remission durations, the disease is reported to have a median survival of only three to five years.4 The clinical features predicting poor prognosis in MCL are generally similar to that of other non hodgkins lymphoma. In our study, there was a high overall incidence of MCL along with majority of cases showing B symptoms. There is a sparse literature about MCL in this part of India. Hence, histomorphology remains the backbone in its diagnosis due to limited availability of IHC and cytogenetic studies in the northeastern region of India. It is crucial to strengthen our diagnostic abilities because without the definitive and targeted therapies MCL will continue

being one of the worst forms of non hodgkins lymphoma.

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