

## Mantle cell lymphoma – a clinicopathological study of 13 cases

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### Abstract

Mantle cell lymphoma is an uncommon non-Hodgkin's lymphoma. In a period of four years, 13 cases of mantle cell lymphoma were diagnosed in our department, comprising 3.1% of all non-Hodgkin's lymphoma diagnosed. The mean age of presentation was 52 years with a slight male preponderance. The disease was nodal in twelve and extra-nodal in tonsil in one. Five patients had bone marrow involvement. Five cases showed a nodular pattern on lymph node biopsy while the remaining eight had a diffuse pattern. Immunophenotyping showed positivity for CD20 and cyclin D1. Despite certain morphological similarity to other low-grade lymphomas, mantle cell lymphoma has a characteristic appearance of its own. It is more aggressive than other low-grade lymphomas and hence needs to be accurately diagnosed.

**Key words:** Mantle cell lymphoma, non-Hodgkin's lymphoma, cyclin D1, mantle cell leukaemia

### INTRODUCTION

Mantle cell lymphoma (MCL) has been recognized as a non-Hodgkin's lymphoma (NHL) of B-cell type with a distinct clinicopathological profile.<sup>1</sup> It is derived from a subset of naïve pregerminal centre cell or the mantle zone of secondary follicles.<sup>1,2</sup> It is relatively uncommon accounting for 5% of malignant lymphoma in North America and Europe<sup>3</sup> and 2.1% of all NHL in India.<sup>4</sup> In 1994, MCL was incorporated in the Revised European American Classification (REAL) of lymphoid neoplasms.<sup>5</sup> Clinically it is considered as a malignant lymphoma of intermediate grade. The histological appearance of MCL has been well described but the diagnosis can be problematic due to morphological overlap with other low grade lymphomas including follicular lymphoma, small lymphocytic lymphoma and marginal zone lymphoma.<sup>1,6-8</sup> Immunohistochemistry and cytogenetic studies act as useful adjuncts. An accurate diagnosis of MCL is important since its clinical course is more aggressive than any other low grade B-cell lymphoma.

The present study describes the clinicopathological features of thirteen cases of MCL in our centre and highlights the problems encountered in the morphological diagnosis.

### MATERIALS AND METHODS

This retrospective study comprises thirteen cases of MCL diagnosed over a period of four years

(1999-2002) in our institute. All cases were documented by biopsy material of an involved node or of an extranodal involved area.

Detailed clinical information was recorded from the case sheets. This included the age and sex of the patients, duration of illness, site of biopsy, distribution of the disease, presence or absence of B symptoms, complete blood counts and bone marrow aspiration and trephine biopsy findings.

Haematoxylin and Eosin (H&E) stained sections were studied and the following histological features evaluated:

- pattern of growth
- morphology of the cells and their relative preponderance
- number of mitotic figures per 10 random high power field (HPF)
- capsular and extra capsular involvement
- presence or absence of residual reactive follicles

Subsequently, immunohistochemistry was done on APES (3-amino propyl triethoxy silane) coated slides. The following antibodies were used: CD3, CD20, CD43 and cyclin D1 (DAKO, Denmark). Immunohistochemistry was performed by avidin biotin peroxidase method with pretreatment by microwave heating. All cases of lymphoma diagnosed in our institute are routinely sent to a National Lymphoma Registry, Tata Memorial Hospital, Mumbai for accrual and confirmation of diagnosis. Immunostaining for CD 43 and cyclin D1 was performed there.

The diagnosis of MCL was based on standard criteria.<sup>6</sup> The histopathological findings on H&E stained sections were reviewed and correlated with the final diagnosis of MCL.

**RESULTS**

Between 1999 and 2002, 420 cases of NHL were diagnosed in our institute. The thirteen cases of MCL, thus accounted for 3.1% of all NHL in this study period.

The clinical characteristics of the thirteen cases are summarized in Table 1. The mean age of presentation was 52 years. There was a slight male preponderance (M:F= 1.2:1). Most patients (84.5%) had generalised lymphadenopathy and/or hepatosplenomegaly or marrow involvement representing advanced disease. Systemic B symptoms were seen in 23% of cases. In one case the primary site of lymphoma was extranodal in tonsil while in the rest it was nodal. Lymphadenopathy was generalized in 77% of cases. Epirochlear and intra-abdominal lymph node involvement was seen in 15.5% and 23% of cases respectively. Hepatomegaly was seen in 23% and splenomegaly in 38.5% of cases. In all the cases with splenomegaly, the size of the spleen was more than 10 cms below the costal margin.

*Histological findings*

At low power, the affected lymph nodes showed complete effacement of normal architecture. Five cases showed a vaguely nodular pattern, which was appreciated at a low magnification with the condenser kept low. In one of these cases, residual reactive follicles were seen focally. The remaining eight cases had a diffuse pattern.

On higher magnification, the neoplastic population was seen to be monomorphic and composed of small lymphocytes with scanty cytoplasm. The nuclei were irregular and cleaved (Fig 1). Lesser number of cells with more rounded nuclei were noted. Nucleoli were inconspicuous in most. Mitotic figures ranged from 5 to 20 per 10 HPF. In one case, there was a mixture of larger cells with vesicular nuclei and prominent nucleolus resembling blasts but they were few in numbers. Capsular involvement was noted in four cases.

Scattered histiocytes with granular eosinophilic cytoplasm were commonly seen. Tingible body macrophages were not conspicuous. Polymphocytes and proliferation centres were not seen. Almost all cases showed prominent hyalinized blood vessels. The differential diagnoses that were considered included small lymphocytic lymphoma - low grade in four cases, follicular lymphoma in two

**TABLE 1: Clinicopathological features of 13 cases of mantle cell lymphoma**

No.	Age/ Sex	Nodal/ extranodal	Liver	Spleen	B symptoms	Peripheral Blood	BM	Pattern
1	60M	Gen LN	-	-	-	-	-	Nodular
2	73M	Gen LN	4 cm	15 cm	+	+	+	Nodular
3	60M	Gen LN	-	-	-	-	-	Diffuse
4	65M	Cervical LN	-	-	-	-	-	Diffuse
5	55M	Gen LN	-	12 cm	-	+	+	Nodular
6	45F	Gen LN	-	10 cm	-	-	-	Diffuse
7	65M	Gen LN	4 cm	15 cm	-	-	-	Diffuse
8	63M	Cervical LN	-	-	-	-	-	Nodular
9	56F	Gen LN	-	-	+	-	+	Nodular
10	40F	Axillary LN	-	-	-	-	-	Diffuse
11	35F	Tonsil	-	-	-	-	-	Diffuse
12	35F	Gen LN	-	-	-	+	+	Diffuse
13	35F	Gen LN	5 cm	12 cm	+	+	+	Diffuse

Key: BM = Bone marrow involvement, Gen LN = Generalised lymphadenopathy, + = Present, - = Absent

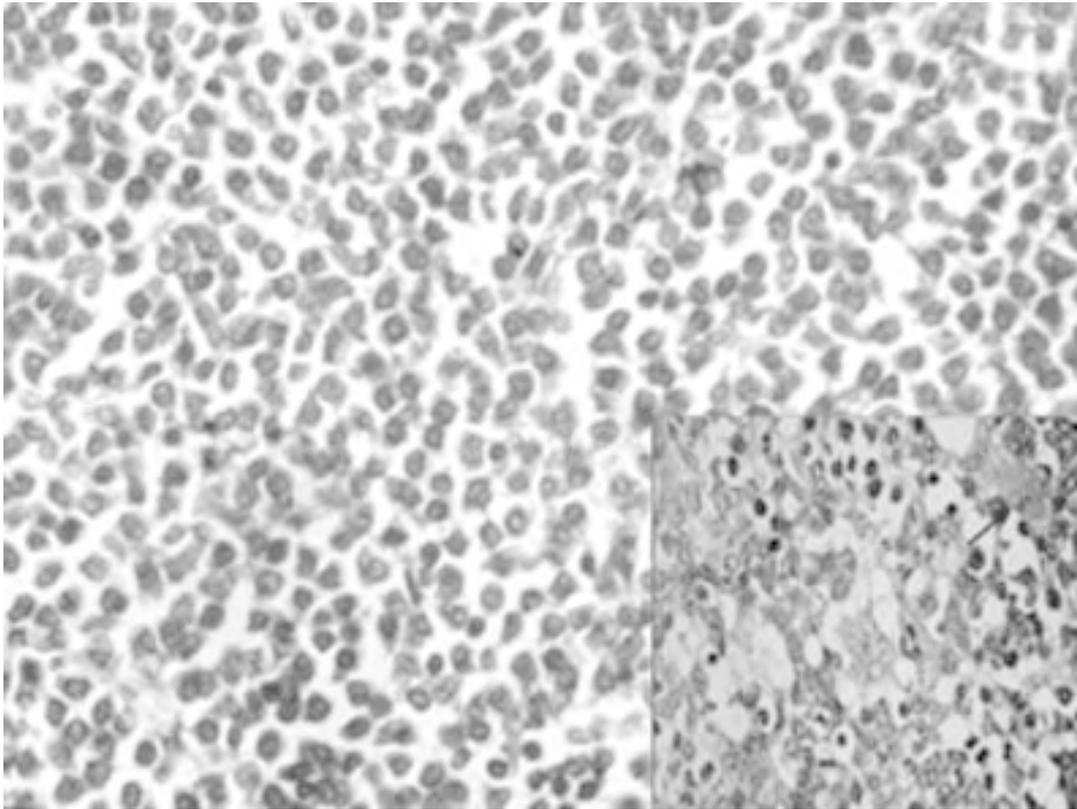


FIG. 1: Low power view showing diffuse pattern of monotonous population of small cells (H&E X 200). Inset shows a higher magnification of the cells with arrow pointing to a histiocyte.



FIG. 2: Cyclin D1 positivity in tumour cells (Streptavidin-Biotin-peroxidase X 400)

and large cell lymphoma in one. In six cases diffuse small-cleaved lymphoma of intermediate grade was considered, a possibility of mantle cell lymphoma being kept in mind. Immunohistochemistry was done in all cases.

#### *Immunohistochemical findings*

All cases were positive for CD20 and negative for CD3. Cyclin D1 was positive in all cases (Fig 2). CD 43 was positive in four of the six cases in which it was done.

#### *Peripheral blood findings*

Complete blood counts were available in all cases. Four cases showed absolute lymphocytosis with circulating lymphoma cells. The cells were polymorphous, small to medium sized with slightly irregular, eccentric nucleus and fine chromatin. Some cells showed a single nucleolus. A thin rim of gray blue cytoplasm was seen (Fig 3).

#### *Bone marrow aspiration and biopsy findings*

Bone marrow aspiration was done in all cases. Trepchine biopsy was done in nine cases. Bone

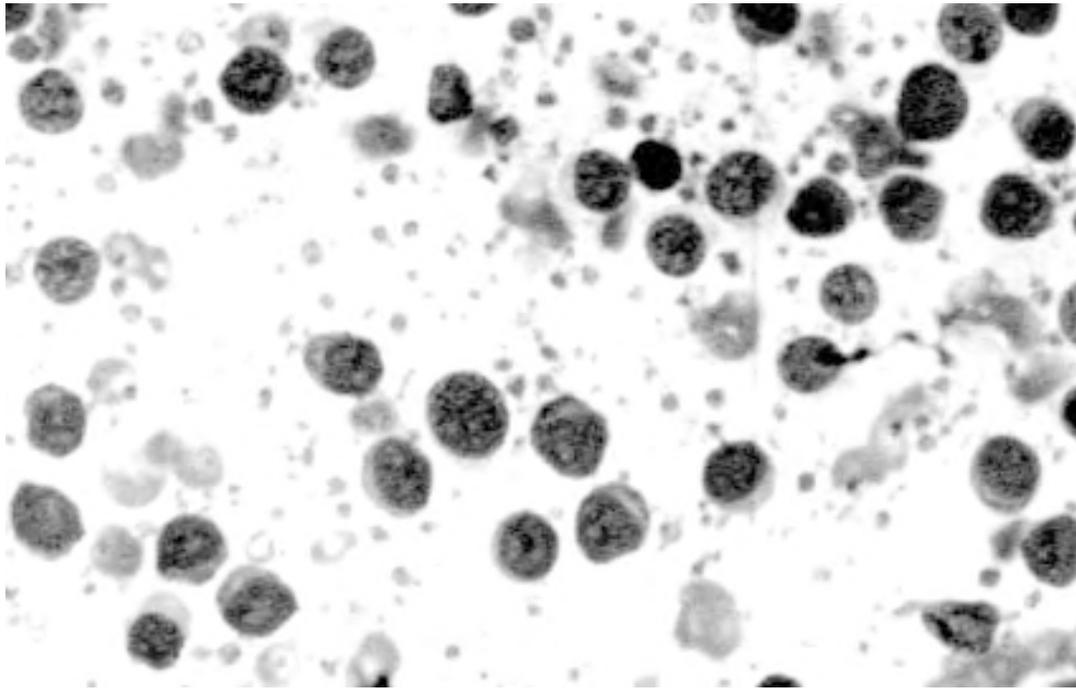


FIG. 3: Peripheral blood film showing mantle cell leukaemia (Leishman X 400)

marrow involvement was noted in five cases. In one case, the peripheral blood did not show leukaemia. Lymphoma cells constituted 10% to 76% of the marrow cells. In three of these five cases trephine biopsy was done and showed marrow infiltration. Two cases had paratrabeular and interstitial infiltration while it was diffuse in another. The details of the peripheral and bone marrow findings are given in Table 2.

**DISCUSSION**

The differentiation of MCL from other B-cell lymphomas has been a gradual and relatively

recent phenomenon. Older terminology for this lymphoma included centrocytic lymphoma in the Kiel classification<sup>9</sup> and intermediately differentiated lymphocytic lymphoma in the modified Rappaport terminology.<sup>10</sup> In the working formulation for clinical usage it falls under small-cleaved cell lymphoma of intermediate grade.<sup>11</sup> Banks *et al* delineated the characteristic morphological, immunophenotypic and genetic profile and proposed the term mantle cell lymphoma.<sup>6</sup> It was subsequently incorporated in the REAL classification in 1994.<sup>5</sup> MCL is relatively uncommon, comprising of 2-8% of NHL in the United States.<sup>8,12,13</sup> In a study

**TABLE 2: Hematological parameters in five patients with peripheral blood and bone marrow involvement**

Case No.	Peripheral blood findings		BM aspiration	BM biopsy
	TLC (X10 <sup>9</sup> /L)	% lymphoma cells	% lymphoma cells	Pattern of infiltration
1.	19.8	60	76	Diffuse
2.	22.5	57	50	ND
3.	9.2	0	35	Interstitial
4.	10.9	44	10	Interstitial & paratrabeular
5.	11.0	70	25	ND

TLC =Total leucocyte count, ND = not done

by Naresh *et al* on the regional distribution of various lymphoid malignancies in India, the incidence of MCL ranged from 0% to 4.6%.<sup>4</sup> In the present study, MCL comprised of 3.1% of all non-Hodgkin's lymphoma diagnosed in four years.

MCL is more common in males and tends to affect older individuals, the mean age of diagnosis being 60 years.<sup>3,14,15</sup> A point of interest in our study was that the mean age in females was 42 years, much less than in males in whom it was 63 years.

Most patients with MCL present with disseminated disease and generalized lymphadenopathy.<sup>1,3,7,8,12,15</sup> The spleen is involved in half the cases and may be the only site of the disease.<sup>16</sup> It is usually more than 1000 grams in weight. In the present study, all the five cases with splenomegaly had massive enlargement of spleen. In about 25% of cases the primary site may be extranodal.<sup>3</sup> Involvement of Waldeyer's ring is reported in 10-15% cases.<sup>1,7</sup> One of our cases had a primary tonsillar MCL. The involvement of gastrointestinal tract in the form of lymphomatous polyposis is also known.<sup>13</sup> We did not encounter any such case though intra-abdominal nodes were present in 23 % cases.

Patients with MCL have frequent bone marrow involvement.<sup>7</sup> Cohen *et al* studied 46 patients with MCL and found 83% had marrow involvement.<sup>17</sup> The very high rate was probably due to bilateral bone marrow biopsies being done. In the present study 38.5% had bone marrow infiltration. The pattern of infiltration in marrow is usually paratrabecular and interstitial.<sup>18</sup> Morphological features of the lymphoma infiltration may suggest MCL but definite diagnostic features allowing separation from other low-grade lymphoma infiltration may be difficult.<sup>18</sup> Paratrabecular infiltration is almost never seen in chronic lymphocytic leukaemia (CLL) making it an important point in the differential diagnosis. Paratrabecular infiltration has classically been described in follicular lymphoma infiltration but one must include infiltration by MCL as a possibility in all such cases.<sup>17,18</sup>

In about 25% of cases patients present with leukaemia.<sup>7,16-20</sup> Mantle cell leukaemia is characterized by an absolute lymphocyte count in excess of  $4 \times 10^9/l$ .<sup>16</sup> The leukaemic phase may infrequently present without lymphadenopathy, in which case it becomes difficult to differentiate from CLL and other low-grade lymphoma infiltration.<sup>16,20</sup> Recognition of the leukaemic

phase is also important because it indicates poor prognosis.<sup>3,14</sup> Wong *et al* described four cell types in mantle cell leukaemia (1) mixture of small to medium-sized cells, (2) predominantly medium-sized cells, (3) predominantly large cells, and (4) giant cells.<sup>19</sup> Sometimes the cases may be mistaken for prolymphocytic leukaemia. The variability of the size of cells has been emphasized by authors.<sup>19,20</sup> The distinguishing features from CLL are the heterogeneous population of cells, pronounced nuclear irregularity, less clumped chromatin and scant rim of cytoplasm.<sup>19</sup> In two of our patients with leukaemic phase a mistaken diagnosis of CLL was made prior to the tissue diagnosis of MCL.

Three histological patterns are found in MCL.<sup>1</sup> Most cases have a diffuse pattern. Less commonly, neoplastic cells are arranged in vague nodules. In a minority of cases there is a widened mantle zone surrounding reactive follicles. Such a pattern is known as mantle zone lymphoma.<sup>1,14</sup> In our study, 61.5 % showed diffuse and 38.5% a nodular pattern. Mantle zone pattern was not seen in any case though one case showed focal preservation of residual follicles. The histopathological growth pattern does not seem to have any prognostic impact<sup>3,7</sup> though a zonal pattern may behave more indolently.<sup>14</sup>

In classical MCL, the neoplastic cells are monotonous.<sup>1,15</sup> Nuclei are small to medium-sized, have nuclear membrane indentations and have inconspicuous nucleoli. Some cells with round nuclei are noted. Cytoplasm is sparse. When evaluating a lymphoma with a nodular pattern, a mixture of large noncleaved lymphocytes and smaller angulated cells favour a diagnosis of follicular lymphoma. Nuclear irregularities and absence of large prolymphocytes, paraimmunoblasts and proliferation centres distinguish MCL from a small lymphocytic lymphoma. The cellular monotony is an important feature of most cases of MCL.<sup>1,15</sup> Epithelioid histiocytes and sclerosed blood vessels are commonly present and are important clues to the diagnosis.

It is now being recognized, however that MCL shows greater morphological heterogeneity than originally described.<sup>6,7</sup> Transformation to a high-grade blastic form has been described.<sup>21,22</sup> The cells are slightly larger with scanty cytoplasm. Nuclei have fine chromatin and resemble lymphoblasts. Mitotic rate is generally very high. One of our cases had blast like cells but they were few in number. Mitosis was also high in these areas. This case had a leukaemic component as well. When this transformation

occurs focally, the area of the larger cells can mimic, at low magnification, proliferation centres of small lymphocytic lymphoma. Close attention to the nuclear irregularity and absence of polymorphocytes and immunoblasts are helpful in making the distinction. Blastic form is associated with a more aggressive course<sup>3, 21</sup> though there are reports to the contrary as well.<sup>22</sup>

Typically the neoplastic cells are CD5, CD20 and bcl2 positive monoclonal B cells with strong surface IgM and IgD but are negative for CD23, CD10, CD11c and CD25. CD43 may be expressed in 60% cells.<sup>1,7</sup> The overexpression of cyclin D1 is highly characteristic and is observed in 90% of cases.<sup>1</sup> The cytogenetic hallmark is a balanced chromosomal translocation between the long arm of chromosome 11 and 14, t(11;14)(q13;32). It must however be recognized that neither cyclin D1 nor the t(11,14) is specific for MCL.<sup>7</sup> MCL is a unique NHL that can be identified solely on morphological features with IHC being helpful in supporting the diagnosis and only mandatory in those uncommon cases with morphological variation.<sup>15</sup>

MCL is generally more aggressive than other small B cell lymphomas. Argatoff *et al* reported an overall survival of 43 months. They noted that performance status, increased mitotic rate, prominent blast morphology and peripheral blood involvement adversely affected the prognosis.<sup>3</sup> It is important to carefully look for and appreciate the morphological features that separate MCL from other non Hodgkin's lymphomas since morphology remains the gold standard for most diagnostic pathologists. This is especially true in a developing country like ours where facilities for immunohistochemistry may not be routinely available.

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