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Original Research Article

MANTLE CELL LYMPHOMA: AN IMMUNOMORPHOLOGIC STUDY WITH DETECTION OF TRANSLOCATION (11;14)(q 13;q32) BY FLUORESCENT IN SITU HYBRIDIZATION FROM A TERTIARY CANCER CARE CENTER

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Abstract

Background: Mantle cell lymphoma is a rare neoplasm of mature B cells forming 5-7% of non-Hodgkin lymphoma. This observational study evaluates the immunomorphologic features of mantle cell lymphoma with detection of translocation (11;14)(q13;q32) by dual fusion interphase Fluorescent in situ hybridization(FISH) at a tertiary cancer center. **Materials and Methods:** Interphase FISH for t(11;14) with dual fusion probes was carried out on 69 cases of de novo mantle cell lymphoma over period of 5 years with adequate representative tissue in paraffin blocks. Immunomorphologic and FISH findings were correlated with clinical data. **Results:** Mantle cell lymphoma formed 5.8% of NHL with male predominance and most presenting with advanced disease. Mean age at presentation was 58 years and affected females at slightly younger age. Cervical lymphadenopathy was the commonest presenting feature, followed by involvement of the gastrointestinal tract. There were 56(81.2%) cases with classic and 13(18.8%) cases with blastoid/pleomorphic morphology.Ki67 proliferation of more than 30% was seen in 53(76.8%) cases and was 30% or less in 16(23.2%) cases. Dual fusion signals on FISH identified t(11;14) in 69 cases and atypical patterns with extra CCND1 copies and more than two fusions were seen in 18 cases, most often in blastoid/pleomorphic variants. **Conclusion:** This study highlights the distinctive clinical, immunomorphologic and genetic findings in mantle cell lymphoma. Interphase FISH on formalin fixed paraffin sections is a useful technique for identification of t(11;14) . Atypical FISH patterns are more often seen in aggressive variants like blastoid and pleomorphic mantle cell lymphoma.

INTRODUCTION

Mantle cell lymphoma (MCL) is a rare distinctive type of non Hodgkin lymphoma (NHL) with unique morphologic, immunophenotypic, cytogenetic and molecular features which forms about 5-7% of all NHL.[1,2] It is a mature B cell neoplasm believed to arise from the cells residing in the follicular mantle zones and characterized by the genetic hallmark viz. translocation(11;14)(q13;q32) which juxtaposes CCND1 gene on chromosome11q13 with IGH on chromosome 14q32, resulting in overexpression of cyclin D1 and leading to cell cycle dysregulation. CCND1/IGH translocation is seen in more than 95% cases.[3,4,5]Recently an indolent leukemic non nodal mantle cell lymphoma and a precursor in situ mantle cell neoplasia have been included in the spectrum of mantle cell neoplasms and all of them are characterized by overexpression of cyclinD1.[1,5] MCL can show a variety of growth patterns, and occasionally have blastoid or pleomorphic morphology with aggressive behavior.[2,3,4,5] FISH has emerged as a very useful method for identifying t(11;14) in the neoplastic lymphoid cells in MCL.[6,7]

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The objective of the present study was to detect the characteristic t(11;14) by interphase FISH on formalin fixed paraffin embedded sections(FFPE) and its correlation with clinicopathological and immunohistochemical findings in MCL.

MATERIALS AND METHODS

This is an observational study of MCL diagnosed over a period of 5 years from 2013- 2017 from a tertiary care cancer center. Clearance was obtained for the study from the Institutional scientific and ethical committee. All the Hematoxylin and Eosin stained and IHC slides from routinely processed FFPE sections were reviewed.

There were seventy six(76) IHC confirmed de novo MCL cases during this period and the present study was done with additional FISH Test along with immunomorphological study. FISH could be done successfully in 69 cases which were included in the present study. Five cases had absent or inadequate tissue in paraffin blocks and two had uninterpretable signals, which were excluded from the study.

Immunohistochemistry (IHC) was carried out using HRP polymer method, with 3,3'-diaminobenzidine tetra hydrochloride (DAB) as chromogen. FFPE tissue blocks were sectioned at 4 micron thickness and taken on silane coated slides, dewaxed and heat induced antigen retrieval was done using the multi-epitope retrieval system (MERS), blocked with 2% skimmed milk blocking solution and then incubated with a primary antibody. The bound primary antibody was detected by the addition of secondary antibody conjugated with HRP polymer and DAB chromogen. The slides were counterstained with hematoxylin and covered in a mounting medium. The following panels of antibodies were usedbased on the differential diagnosis on histomorphology: LCA, CD20, CD3, CD5, CD23, Cyclin D1, SOX11, Ki67, CD10, BCL2, BCL6 and Tdt. Positive and negative controls were used along with test samples.

Interphase FISH was carried out on paraffin embedded tissue sections of 4-5 micron thickness which were deparaffinised by warming for 1 hour at 65°C and by xylene immersion (3 changes of 10 min at 40 degrees). After dehydration, they were placed in 0.2N HCl bath for 20 min at room temperature for hydrolysis and washed in saline sodium citrate (SSC) for 5min each at room temperature and at 37 degrees. After pre treating the sections in sodium thiocyanate at 80 degrees for 35 minutes, the sections were digested in protease solution at 37 degrees for 15 minutes. The sections were washed in SSC before and after placing in neutral buffered formalin for 10 minutes at room temperature. Slides were dehydrated, air-dried and denatured in 70% formamide in SSC for 7 minutes at 75 degrees in thermobrite. After dehydration and air drying, CCND1/IGH dual fusion probes (red labelled probe flanking CCND1 breakpoint at 11q13 and green labelled probe flanking IGH breakpoint region at 14q32,Cytocell, Oxford Gene technology, Cambridge UK) was added to the target area. Co-denaturation was performed in the Hybrite at 75°C for 5 minutes followed by hybridisation at 37 degrees for 18 hours. Counter staining with DAPI was done after washing the sections in NP40 in SSC. Cells were viewed using fluorescent microscope (Olympus, USA) with appropriate filters. The FISH patterns were interpreted after 100 nuclei were counted. A specimen was classified as abnormal and consistent with IGH-CCND1 fusion if the number of nuclei observed with t(11;14) double fusion pattern was seen in at least 10%of the nuclei.

Statistical Methods

Data were analysed using SPSS version 22. Independent sample t test was used to compare continuous data and chi square is used to test the association between categorical variables. Kaplan-Meier method of survival analysis with Log Rank test is used to compare survival curves and p value of <0.05 was considered significant. Overall survival (OS) was defined as the period from diagnosis to death from any cause.

RESULTS

Demographic features: MCL formed 5.8% of a total of 1397 cases of NHL and there were 56 males and 13 females with an M:F ratio of 4.3:1 showing a male predominance. The patient's age ranged from 30-87 years with a mean age of 58 years. Mean age for males was 60 years which was higher as compared to mean age for females which was 54 years.Lymph nodes(55 cases/79.7%)were the commonest site involved with cervical lymphadenopathy as the most frequent presentation and extranodal disease was seen in 14(20.3%) most often involving the gastrointestinal tract (6cases/8.7%).The sites of disease at presentation are given in Table1. Bone marrow was involved in 29(42%) cases and peripheral blood involvement in 12(17.4%) cases of MCL.

Morphology: Fifty six(81.2%)cases showed classic morphology with uniform small to medium sized neoplastic cells having scanty cytoplasm with irregular nuclear contours and inconspicuous nucleoli. Diffuse, nodular and mantle zone pattern of neoplastic lymphoid infiltrate was seen in 39(56.5%), 21(30.4%) and 6(8.7%) cases respectively, and combined diffuse and nodular pattern was seen in 3(4.4%) cases. Morphologic clue to the diagnosis of MCL were the scattered pink histiocytes. Thirteen (18.8%) had blastoid /pleomorphic morphology with uniform blast like neoplastic cells in 10 blastoid cases having either coarse nuclear chromatin and brisk mitoses (30-40 mitoses/10hpf) and large cells having irregular nuclei and prominent nucleoli in 3 pleomorphic cases.

IHC findings: All 69 cases showed intense and strong expression of CD20, BCL2 and Cyclin D1. Immunostaining for Tdt was done in all cases with

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blastoid morphology to rule out lymphoblastic lymphoma and was found to be negative, in addition positive immunostaining for Cyclin D1 and SOX11 helped in establishing the diagnosis in these cases. CD23 was positive in two cases and CD10 was negative in all 69 cases. Ki-67 proliferation was assessed by eye balling in representative areas of at least 5 high power fields, according to the consensus guidelines of the European MCL network.[8]Sixteen(23.2%) had Ki-67 proliferation of ≤ 30% and 53(76.8%) had more than 30% proliferation. Ki-67 proliferation in blastoid MCL ranged from 70-90% and 60- 70% in pleomorphic MCL(Figure 1A inset).Neoplastic lymphoid cells expressed CD5 in all but one case and staining was less intense as compared to adjacent T lymphocytes (Figure 1D). SOX11 immunoreactivity was seen in 64(92.8%) cases and 5(7.2%) were negative. Staining for SOX11 was heterogeneous with high expression in 34(53.1%) and low expression in 30 (46.9%) cases. (Figure 2A, B)

FISH results: FISH for CCND1/ IGH fusion for t(11;14) with satisfactory signals were seen in 69 cases(56 classic and 13 blastoid/pleomorphic MCL).Finding dual fusion in more than 10% of cells was considered positive.[6,7] , while normal lymphoid cells showed two separate red and green signals(Figure2C). Typical dual fusion (2Fusion1Red1Green, 1Fusion2Red1Green or 1Fusion1Red2Green) was seen in 51(73.9%) cases (Figure 2D) and in 18(26.1 %) cases atypical signals were seen which included multiple fusion signals and extra copies of CCND1 along with fusion signals(Figure 2E&F). Atypical signal patterns accounted for 61.5% (8 of 13) of blastoid and pleomorphic cases andonly 17.9%(10 of 56) of classical MCL which was statistically significant(p value-0.007). Half of blastoid(5 of 10) MCL showed atypical signal pattern (more than 2 fusion signals in 3 cases and extra copies of CCND1 in 2 cases). All 3 cases of pleomorphic MCL showed atypical pattern with extra fusion signals (Figure 3).

Out of 69 cases treatment details were available in only 33cases. Seven (21.2%) patients had stage I/II disease and 26 (78.8%) patients had stage III/IV disease. Seventeen (51.5%) patients had B symptoms .Mantle cell lymphoma International Prognostic Index(MIPI)was calculated as described by Hoster et al.[9], 12 cases had high risk,10 had intermediate risk and 11 had low risk disease. Increased serum LDH levels were seen in 20(60.6%) patients and12(36.4%) had increased total leucocyte count. The main clinicopathological features are summarized in Table II.

Treatment was not uniform due to differences in age, stage, symptoms and treatment era. Twenty one patients received multiagent chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP), five patients received chemoimmunotherapy with four receiving rituximab-CHOP(R-CHOP) and one Bendamustine and Rituximab (BR). Four patients received hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine(HyperCVAD) and three patients were treated with cyclophosphamide, vincristine, procarbazine, predisolone (COPP)regimen. One patient received Involved Field Radiotherapy (IFRT) in addition to CHOP. The follow up ranged from 2 months to 64 months with an average overall survival of 23.3 months. Six patients had complete remission, four patients had complete remission with relapse,18 patients had partial remission and 5 patients died of the disease during chemotherapy.

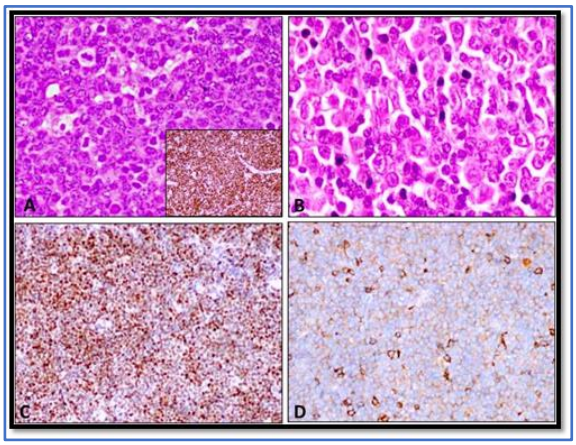

Figure 1. A shows blastoid mantle cell lymphoma with cells having coarse nuclear chromatin and frequent mitoses. (Hematoxylin and Eosin X400) Inset shows very high Ki67 proliferation. (Immunoperoxidase stain X100). B -shows pleomorphic mantle cell lymphoma showing large neoplastic lymphoid cells many having prominent nucleoli. (Hematoxylin and Eosin X400). C- shows nuclear expression of Cyclin D1 (Immunoperoxidase stain X100). D- Shows neoplastic cells with CD5 expression which is less intense than the scattered T lymphocytes (Immunoperoxidase stain X400)

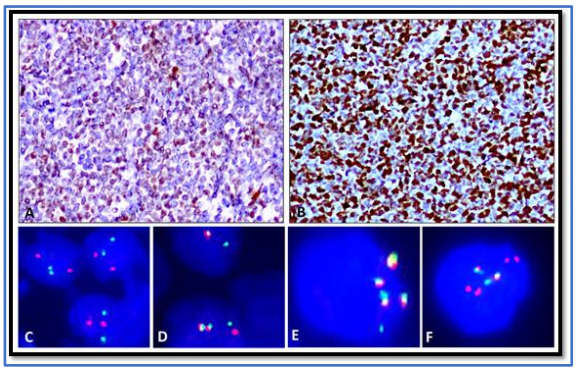

Figure 2.A shows neoplastic lymphoid cell with weak SOX11 expression (Immunoperoxidase stain X400).B- shows neoplastic cells with strong expression of SOX11 (Immunoperoxidase stain X400).C-shows FISH in a normal lymphocyte with two red and two green signals. D- shows FISH with typical dual fusion representing t(11;14)and one red and one green signal in MCL. E- shows atypical FISH pattern in pleomorphic MCL with multiple fusion signals. F shows atypical FISH pattern in blastoid MCL with extra red/CCND1 signals.

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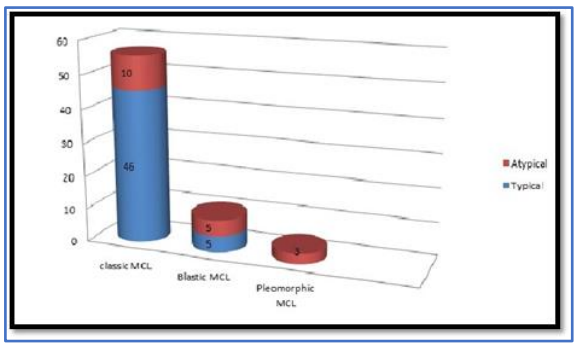

Figure 3. Shows the frequency of typical and atypical FISH patterns in classical, blastoid and pleomorphic MCL.

Table I: shows the sites of involvement of MCL at presentation

Site	No of cases (69)*
Cervical lymph node	44
Inguinal lymph node	04
Axillary lymph node	03
Epitrochlear lymph node	01
Tonsil and Waldeyer's ring	04
Retroperitoneal lymph nodes	03
Stomach	03
Ileocecal	01
Colon	01
Rectum	01
Chest wall	02
Eyelid	01
Paravertebral mass	01

*Note: Six cases presented with involvement of more than one site.

Table II: Clinicopathological characteristics of Mantle cell lymphoma

Age Mean age -males Mean age -females Age>60 years	60years 54 years 29(38%)
M:F ratio	4:1
Histologic subtype Classic Blastoid Pleomorphic	 56(81.2%) 10(14.5%) 3(4.3%)
Pattern Diffuse Nodular Mantle zone pattern Combined	 39(56.5%) 21(30.4%) 6(8.7%) 3(4.4%)
CD5 negative	1(1.4%)
CD23 positive	2(2.9%)
SOX11 positive	64/69(92.8%)
SOX11 negative	5/69(7.2%)
Ki67 30% or less	16(23.2%)
Ki67>30%	53(76.5%)
Bonemarrow involved	29(42%)

Table III: Distribution of Typical and atypical fusion patterns by FISH in MCL

Type of MCL	Typical fusion pattern Number of cases	Atypical fusion pattern Number of cases	Total
Classic	46(82.1%)	10(17.9%)	56
Blastoid	5(50%)	5(50%)	10
Pleomorphic	0(0%)	3(100%)	3
Total	51(73.9%)	18(26.1%)	69

DISCUSSION

MCL is a mature B cell neoplasm arising from the naïve cells residing in the follicular mantle zones and characterized by the genetic hallmark t(11;14)(q13;q32) resulting in overexpression of cyclin D1.[1,2] The evidence to date supports the t(11;14) and cyclin D1 overexpression as the initial or very early event in MCL and require additional molecular events for malignant transformation.[10]Recent studies have shown that MCL is a heterogeneous disease with a subset of leukemic non-nodal presentation having better prognosis and blastoid/pleomorphic variants showing an adverse outcome.[2,5,10] Other adverse pathologic and clinical prognostic factors include diffuse pattern

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of growth, high Ki67,blastic morphology, CD 5 expression, SOX 11 expression, p53 mutation and MIPI.[8,9,11,17] FISH assay is very useful in confirming the diagnosis of MCL, has wide applicability as it may be performed on both paraffin-embedded and fresh tissue[18].There are very few large scale studies of MCL from India due to relative rarity of the disease and this is the first Indian study to incorporate analysis of FISH findings for t(11;14).

We studied the clinicopathological and immunophenotypic features of 69 cases of MCL and interphase FISH with dual fusion probes for t(11;14) was carried out in all 69 Cases. MCL formed 5.8% of cases of NHL with a male preponderance(M: F ratio 4:1) which is similar to the studies by Gujral et al.[19], Das et al.[20] and Roy et al.[21] from India and the world literature.[19-26]The average age at presentation in the present study was 58 yrs (range 30 to 87 yrs), similar to studies from India and other Asian countries.[19-24]but lower when compared to western literature where the mean age is around 65years.[25-2]Interestingly the average age for females (54yrs) was lower than that for males(60yrs) in our study which was statistically significant (p value 0.043), however there was no difference in survival between the two groups(20.8 months in females vs. 20.9 months in males). Lymph node involvement(79.7%)was the commonest presenting feature followed by involvement of the gastrointestinal tract(8.7%).Majority (78.8%)of patients had stage III/IV disease and the remaining (21.2%) had stage I/II disease and nearly half (51.5%) had B symptoms at presentation, the above findings are similar to several other studies.[19-26]MIPI is an important indicator of survival in MCL.[9,12,13], and in the present study though MCL with high risk MIPI was associated with poor overall survival as compared to cases with low risk, it did not reach statistical significance(14 months vs 29 months).

Morphologically MCL showed diffuse growth as the commonest pattern (56.5%) followed by nodular (30.4%) and mantle zone (8.7%) patterns with 4.4% having combined diffuse and nodular areas which did not have any prognostic significance. There were 56 classic MCL cases and 10 cases with blastoid morphology and 3 cases with pleomorphic morphology. MCL with blastoid/ pleomorphic morphology have a poorer prognosis compared to classic MCL.[22,29,30] and in the present study eight cases of blastoid/pleomorphic MCL where follow up was available showed poor overall survival(17.3 months vs. 28.3 months).Ki 67 proliferation is one of the important indicators of prognosis with proliferation index of more than 30% being associated with poor survival (9-14).Similar result was seen in the present study with improved OS in MCL with 30% or less Ki 67 proliferation.

SOX11 has emerged as a disease specific marker of MCL with a role in pathogenesis, diagnosis and prognosis[16, 31]. Nuclear SOX11 expression was seen in 64(92.8%) of 69 cases with heterogeneous staining, high expression was seen in 34(53.1%) and low expression was seen in 30(46.9%) cases. However the presence or absence of expression or the intensity of SOX11 expression had no bearing on the overall survival of MCL patients in the 33 cases where follow up was available in the present study. The prognostic significance of SOX 11 expression in nodal MCL has varied with some studies showing better prognosis, some with poor outcome and some without any prognostic significance.[16, 32,33,34,35]

There was one patient with CD5 negative MCL in the present study with follow up, who had favorable outcome with OS of 46 months, which is consistent with findings of other studies of CD 5 negative MCL.[17,36]

Interphase FISH showed abnormal fusion signals indicative of t(11,14) in all 69 cases with adequate tissue in paraffin blocks. Atypical FISH patterns of more than 2 fusion signals and/or extra copies of CCND1 were more often seen in the more aggressive blastoid (5 of 10 cases) and pleomorphic (3 of 3 cases) MCL as compared to classic MCL (10 of 56 cases)which was statistically significant(p value-0.007).Atypical FISH pattern in association with blastoid and pleomorphic MCL is usually associated with poor overall survival.[37,38] however in the present study there was no statistically significant difference in the overall survival between typical and atypical FISH patterns.

CONCLUSION

MCL is a disease predominantly of elderly males and affected females at a younger age in the present study. SOX11 staining was heterogeneous in neoplastic cells and was complementary to cyclin D1 for diagnosis of MCL, however the staining intensity had no effect on survival. FISH is a very useful tool to identify t(11;14) in paraffin embedded sections and is complementary to IHC for the diagnosis of MCL especially blastoid and pleomorphic variants from morphologic mimics. Atypical FISH patterns were frequently seen in blastoid/pleomorphic MCL. The limitation of the present study was lack of treatment details and follow up in all cases. However in the 33 cases where follow up was available, high MIPI, blastoid/pleomorphic morphology and high Ki67 had negative prognostic impact.

Disclosure

All authors have no financial disclosures and declare no conflicts of interest.

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