

The Pestilential Pallium- Mantle Cell Lymphoma

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Abstract

Mantle cell lymphoma is a mature B cell lymphoma composed of miniature to intermediate, atypical, monomorphic lymphoid cells. The neoplasm is associated with chromosomal translocation t(11;14)(q13;q32) or IGH/CCND1 along with over expression of cyclin D1 and demonstrates clinically aggressive behaviour. Terminology such as centrocytic lymphoma, lymphocytic lymphoma of intermediate differentiation or mantle zone lymphoma to describe mantle cell lymphoma appears antiquated. Mantle cell lymphoma configures ~10% of non Hodgkin's lymphomas and ~7% of B cell lymphomas. Median age of disease occurrence is 68 years.

Introduction

A male predominance is observed with male to female proportion of 2 to 3:1[1-2]. Mantle cell lymphoma commonly occurs within lymph node, bone marrow, peripheral blood, spleen or hepatic parenchyma. Besides, gastrointestinal tract, Waldeyer's ring, pulmonary parenchyma, pleura, central nervous system or diverse cutaneous surfaces are frequently implicated extra-nodal sites [1-2]. Extra-nodal emergence of mantle cell lymphoma in the absence of lymph node incrimination and enlargement appears in ~15% instances. Mantle cell lymphomadelineates chromosomal translocation t[11-14] along

with IGH/CCND1 genes which activate progression from G1 to S phase of cell cycle [1-2].

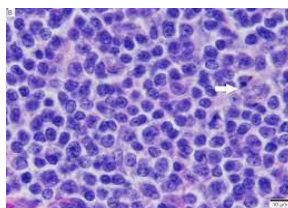


Figure 1: Mantle cell lymphoma composed of monomorphic, atypical lymphoid cells with clumped chromatin and inconspicuous nucleoli with a lack of germinal centres [5].

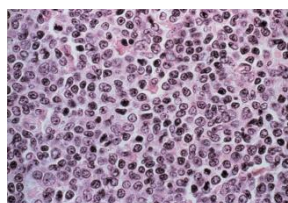


Figure 2: Mantle cell lymphoma delineating monotonous, atypical lymphoid cells with clumped nuclear chromatin, inconspicuous nucleoli and lack of germinal centers [6].

IGHV gene appears non mutated or minimally mutated in majority of neoplasms. Genetic translocation t[11-14] (q13;q32) may be observed. Fluorescent in situ hybridization (FISH) may be conveniently performed upon fixed tissue sections. FISH may delineate genomic rearrangements of cyclin D2 in instances non reactive to cyclin D1-[1-2]. Fresh tissue samples may be subjected to conventional cytogenetic analysis for discerning the lymphoma. Polymerase chain reaction (PCR) assay of mantle cell lymphoma commonly detects a major 'breakpoint region [1-2]. Additionally, secondary chromosomal aberrations may appear as ~gains of chromosomes 3q26, 7p21, 8q24 (MYC) or 13q31~loss of chromosomes 1p13-31, 6q23-27 (TNFAIP3), 9p21 (CDKN2A which encodes for p16 INK4a and p14 ARF) 11q22-23 (ATM), 13q11-13, 13q14-34 or 17p13 (TP53)[1-2].

Mantle cell lymphoma demonstrates pre-germinal centre cell of origin with immune reactive SOX11+ and non mutated IGHV gene. Besides, post germinal centre origin with a subset of neoplasms immune non reactive to SOX11- and hyper-mutated IGHV may be exemplified. Majority (70%) of mantle cell lymphomas manifest stage IV disease at initial representation [1-2]. Mantle cell lymphoma exemplifies distinct subtypes as aggressive disease incriminating lymph nodes, immune reactive to SOX11+ indolent disease with leukemic representation, absence of lymph node involvement and immune non reactive SOX11. Besides, generalized lymphadenopathy, hepatomegaly or splenomegaly may ensue [1-2]. Up to 70% mantle cell lymphomas depict leukemic involvement at initial disease representation. Peripheral blood enunciates atypical lymphoid cells within comprehensive (100%) instances, as discerned by flow cytometry. Multiple intestinal polyps, designated as lymphomatous polyposis may be exemplified [1-2]. Classic mantle cell lymphoma may evolve into blastoid or pleomorphic variant. Aforesaid transformation is encountered in ~one fifth (22%) of relapsed mantle cell lymphoma [1-2].

Cytological examination enunciates a monotonous population of miniature to intermediate lymphoid cells incorporated with distinct, pale to basophilic cytoplasm, nuclear clefts, finely stippled nuclear

chromatin and inconspicuous nucleoli [1-2]. Grossly, incriminated lymph node is enlarged. Cut surface is tan, homogenous and demonstrates or may be devoid of indistinct tumour nodules. Spleen enunciates a generalized, micro-nodular configuration with perivascular tumour infiltration [1-2]. Gastrointestinal tract exhibits foci of lymphomatoid polyposis with multiple lymphoid polyps sprinkled upon small and large bowel. Additionally, mucosal ulcers, tumour nodules and diffuse mucosalthickening may be encountered. Microscopic infiltration of atypical lymphoid cells within diverse viscera in the absence of a grossly visible lesion is commonly encountered [1-2]. Upon microscopy, incriminated lymph node depicts a diffuse, nodular or mantle zone tumour configuration, in decreasing order of frequency. Nodal mantle cell lymphoma appears nodular in > 50% instances whereas diffuse mantle cell lymphoma is nodular in < 50% tumefaction.

Neoplastic nodules are devoid of proliferation centres. Mantle cell lymphoma is composed of monomorphic, atypical lymphoid cells of miniature to intermediate magnitude. Tumour cells display clumped nuclear chromatin, inconspicuous nucleoli and irregular nuclear perimeter [1-2]. Generally, neoplastic cellular component is devoid of centroblasts, immunoblasts or para-immunoblasts. Foci of epithelioid histiocytes may be discerned. Vascular articulations appear hyalinised [1-2]. Mantle cell lymphoma demonstrates distinct subcategories as aggressive variant denominates blastoid mantle cell lymphoma is a monomorphic neoplasm appearing as lymphoblast-like and simulates lymphoblastic lymphoma. Mitotic activity is significant and occurs as >20 mitosis to 30 mitoses per 10 high power fields [1-2].

Results and Discussions

Pleomorphic mantle cell lymphoma consists of enlarged cells with abundant pale cytoplasm, encephalolike nuclei with prominent nucleoli, and irregular perinuclear infiltration. Multinucleated cells are observed. This neoplasm is not monomorphic and resembles diffuse large B-cell lymphoma. Non aggressive variant denominates small cell mantle cell lymphoma is composed of miniature, spherical lymphocytes pervaded with clumped nuclear chromatin, akin to chronic lymphocytic leukaemia [1-2]. Marginal zone-like mantle cell lymphoma is comprised of lymphoid cells permeated with abundant, pale cytoplasm. Neoplasm simulates marginal zone or monocytoid B cells. Few instances depict foci of lympho-plasmacytic differentiation. Follicular dendritic cell (FDC) meshwork enunciates a nodular configuration with primary follicle-like pattern, germinal centre-like pattern or diffuse pattern [1,2]. ~bone marrow infiltrate of mantle cell lymphoma manifests as nodular, interstitial, para-trabecular or an amalgamation of aforesaid tumour configurations. Peripheral blood demonstrates neoplastic configuration akin to tissue samples. Tumour cell nucleoli may be prominent [1-2]. Spleen is infiltrated by mantle cell lymphoma delineates tumour nodules confined to enlarged white pulp along with variable incrimination of red pulp. A residuum of naked germinal centres may ensue. Tumour cells appear monotonous. Foci of marginal zone-like appearance may be discerned in specific instances. Gastrointestinal tract may simulate lympho-epithelial lesions emerging within marginal zone lymphoma [1-2]. Relapse within mantle cell lymphoma enunciates decimated configuration of mantle zone. Neoplastic cells exhibit pleomorphic nuclei of increased magnitude and well dispersed nuclear chromatin. Mitotic activity and Ki67 proliferation index is enhanced. Blastoid mantle cell lymphoma may

relapse with classic morphology [1-2] in table 1 and 2.

Mantle cell lymphoma international prognostic index is composed of clinical parameters as age, performance status as per Eastern Cooperative Oncology Group (ECOG), serum lactate dehydrogenase (LDH) levels and leukocyte count. Thus contemplated, three morphologic groups manifest with significantly divergent prognostic outcomes. Mantle cell lymphoma prognostic index (MIPI) score is suitably adopted to stratify outcomes of neoplastic metamorphosis and progression and is constituted of

- age wherein increasing age is accompanied by unfavourable prognosis.
- serum lactate dehydrogenase (LDH) level is indicative of cellular injury wherein elevated levels are beneficial in detecting mantle cell lymphoma.
- Eastern Cooperative Oncology Group (ECOG) performance status appropriately assesses functional activity of incriminated subjects.
- leukocyte count within peripheral blood is evaluated as 10^3 cells/microliter or 10^3 cells/ μ L or 10^9 cells/litre.
- Ki67 is a cellular marker protein associated with cellular proliferation wherein Ki67 proliferative index in percentage is indicative of neoplastic growth fraction and progression and appears as a component of MIPIb.

Calculation of MIPI is obtained as

MIPI formula = $[0.03535 \times \text{Age (years)}] + 0.6978$ (if ECOG 2-4) + $[1.367 \times \log_{10} (\text{LDH/ULN})] + [0.9393 \times \log_{10}(\text{WBC})]$

ULN (Upper Limit Normal of LDH), WBC (White Blood Cell Count per microliter or $\times 10^6$).MIPI is stratified as

- low risk lymphoma with score between 0 to 3
- intermediate risk lymphoma with score between 4 to 5.
- high risk lymphoma with score between 6 to 11

MIPI score	Disease risk	Median overall survival
<5.7	Low	Not attained
5.7 to <6.2	Intermediate	51 months
≥ 6.2	High	29 months

Table 1: International Prognostic Index score for mantle cell lymphoma [2-3].

MIPIb score	Disease risk	Median overall survival
<5.7	Low	Not attained
5.7 to <6.5	Intermediate	58 months
≥ 6.5	High	37 months

Table 2: Biological International Prognostic Index for mantle cell lymphoma [2-3].

Mantle cell lymphoma is immune reactive to Cyclin D1, CD19, CD20, CD43, CD5, CD21, CD23, SOX11,

MUM1/IRF4, BLIMP or XBP1. Few neoplasms are immune reactive to CD10. Exceptionally, lymphoma may be immune non reactive to CD5 or SOX11 [3-4]. Ki67 proliferative index may be quantified by evaluating mitotic activity within five, independent high power fields. Mantle cell lymphoma may not show immunoreactivity for CD10, BCL6, CD200, or LEF1 [3-4]. Upon flow cytometry, mantle cell lymphoma exhibits specific phenotype as CD5+, CD19+, CD20+, CD22+, CD79b+ or FMC7+ along with monotypic Ig. Besides, CD3-, CD10-, CD11c+/-, CD23-, CD43+/- or CD200-/ immunophenotype may be encountered [3-4]. Exceptionally, mantle cell lymphoma enunciates atypical immunophenotype denominated as CD5- or CD10+, CD200+ or CD23+ (dim instances ~ 10%) [3-4]. Nodal mantle cell lymphoma requires segregation from neoplasms such as chronic lymphocytic leukaemia/ small lymphocytic lymphoma, follicular lymphoma, nodal marginal zone B cell lymphoma, splenic marginal zone lymphoma (SMZL), reactive follicular hyperplasia or hyaline vascular subtype of Castleman's disease [3-4]. Leukemic mantle cell lymphoma mandates distinction from hairy cell leukaemia, chronic lymphocytic leukaemia/ small lymphocytic lymphoma, prolymphocytic leukaemia or lymphoblastic leukaemia [3-4]. Cogent surgical tissue sampling from incriminated lymph node or extra-nodal sites demonstrates monomorphic proliferation of miniature to intermediate B cells which over express cyclin D1 or SOX11(3,4). Chromosomal translocation t(11;14)(q13;q32) or IGH/CCND1 may be discerned [3-4].

Mantle cell lymphoma may be subjected to frozen section examination, cytogenetics, flow cytometry or preparation and evaluation of imprints. Morphological features are akin to microscopy wherein assessment of nuclear magnitude, outline and chromatin configuration aids appropriate distinction [3-4]. Mantle cell lymphoma may exhibit anaemia, thrombocytopenia, elevated lactate dehydrogenase or serum β 2 micro-globulin. Mild quantities of monoclonal serum component may appear [3-4]. Peripheral blood examination of mantle cell lymphoma demonstrates polymorphous cellular component and atypical lymphocytosis. Nuclear magnitude and outline is variable with reticulated nuclear chromatin and prominent nucleoli. On account of atypical peripheral blood lymphocytosis, mantle cell lymphoma may simulate B cell chronic lymphocytic leukaemia [3-4].

Mantle cell lymphoma is appropriately managed with high dose chemotherapy with regimens as hyper CVAD chemotherapy or R-DHAP / R-CHOP. Additionally, autologous stem cell transplantation can be adopted [3-4]. Conventional dose therapy as rituximab (R-CHOP or R-bendamustine) may be employed. Neoplasms inappropriate for conventional dose therapy can be managed with R-bendamustine or R-lenalidomide. Indolent (low risk) mantle cell lymphoma may be subjected to simple observation [3-4]. Additionally, contemporary biologic agents as ibrutinib (Bcr tyrosine kinase inhibitor), idelalisib (phosphoinositide-3 kinase inhibitor), bortezomib (proteasome inhibitor), temsirolimus (mTOR inhibitor) or lenalidomide (immune modulatory agent) may be beneficial in treating mantle cell lymphoma [3-4]. Mantle cell lymphoma is associated with median survival of ~7 years. Inferior prognosis is encountered with histo-pathological or molecular subtypes depicting ~elevated mitotic rate (> 50/mm²) ~Ki67 proliferative index or immune reactive MIB1 > 30% ~blastoid and pleomorphic variant of mantle cell lymphoma ~MYC genetic rearrangement ~TP53 genomic mutation or over expression or loss of chromosome 17p ~CDKN2A deletion (chromosome 9p).

~gain in chromosome 3q, deletion of chromosome 9q [3-4].

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5. Image 1 Courtesy: Libre pathology.
6. Image 2 Courtesy: Lancet oncology.