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Mantle Cell Lymphoma with Negative CCND1 FISH Studies: A Case Report

Sarah Abdul Halim[1], Dhamirah Nazihah Mohd Nasiruddin[1], Mohammad Hudzaifah Nordin[2], Sumaiyah Adzahar[2,3]

[1]Department of Pathology and Laboratory Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, Pahang, Malaysia
[2]Faculty of Medicine, Universiti Sultan Zainal Abidin (UniSZA), Terengganu, Malaysia
[3]Department of Pathology and Medical Laboratory, Faculty of Medicine, Universiti Sultan Zainal Abidin (UniSZA), Terengganu, Malaysia

Corresponding author: srikandimaya11@gmail.com

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Abstract

Mantle cell lymphoma (MCL) is an aggressive B-cell lymphoma characterised by the overexpression of cyclin D1 due to a chromosomal translocation of t (11;14) (q13;q32) in most cases. This abnormal cyclin D1 expression is a key factor in diagnosing MCL. Morphologically, MCL typically manifests as a proliferation of small- to medium-sized cells with irregular nuclear contours. In aggressive variants, such as those comprising lymphoblast-like (blastoid) or pleomorphic cells, the disease course may be more rapid and challenging to manage. Notably, a rare cyclin D1-negative variant of MCL has been identified, characterised by translocations involving CCND2/cyclin D2. We present a case of MCL with negative CCND1/IGH rearrangement, contributing to the broader understanding of the disease's varied manifestations.

Keywords

Mantle cell lymphoma, non-Hodgkin's lymphoma, CCND1, FISH studies

Introduction

Mantle cell lymphoma (MCL) is a neoplasm of mature B-cells representing a rare subtype of non-Hodgkin's lymphoma. This distinct entity accounts for a small percentage of all non-Hodgkin's lymphoma cases, ranging from 2.5% to 10.0%[1]. It is more prevalent in older adult males but can occur in individuals of any age or gender[1,2]. MCL is recognised by its morphological, clinical, immunophenotypic, and molecular genetic features. These characteristics are identified through various tests, including microscopic examination, flow cytometry, immunohistochemistry, and genetic profiling[1] .

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Case report

A 69-year-old Malay lady presented with a history of prolonged cough, loss of weight, and loss of appetite over three months. She reported no dysphagia, hoarseness, or snoring. Oropharyngeal examination revealed a right palatine tonsil enlargement with the uvula deviation to the left side. Bilateral mobile, non-tender cervical lymph nodes were palpable, with the largest measuring about 2cm × 2cm. However, no hepatosplenomegaly was observed. Computed tomography of her neck, thorax, abdominal, and pelvis (CT-NTAP) revealed right palatine tonsil enlargement with intra-abdominal masses and multiple enlarged cervical and intra-abdominal lymph nodes, suspicious of lymphoma.

A complete blood count showed that she had borderline low hemoglobin with normal total white and platelet counts. Her peripheral blood picture revealed no definite abnormal lymphoid cells. Bone marrow aspirate showed 2.6% abnormal lymphoid cells with small to medium size and scanty cytoplasm; some cells have clefted nuclei. The bone marrow trephine biopsy was hypercellular with altered topography and focal infiltration by lymphoma cells exhibiting medium size, dense chromatin, irregular nuclear outline, and round to oval nuclei. These cells were immunoreactive to CD20, CD5, CD23 (weak), BCL2, and Cyclin D1 (Figure 1) but negative for CD10 and CD3. The trephine biopsy concluded bone marrow infiltration by MCL.

Immunophenotyping revealed 0.8% abnormal lymphoid cells gated at low SSC/bright CD45 area. The B cells expressed CD19, CD20, CD5, and CD79b, with lambda light chain restriction but were negative for FMC7, CD200 and CD10. The tru-cut biopsy of the left cervical lymph node was performed and consistent with MCL. Fluorescence in-situ hybridisation using CCND and IGH fusion probe showed negative for CCND1/IGH translocation. Treatment was initiated with a combination of chemotherapy and targeted therapy, including rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), followed by maintenance therapy with rituximab, bendamustine, and cytarabine. The patient responded well to initial therapy, achieving partial remission after six cycles of R-CHOP.

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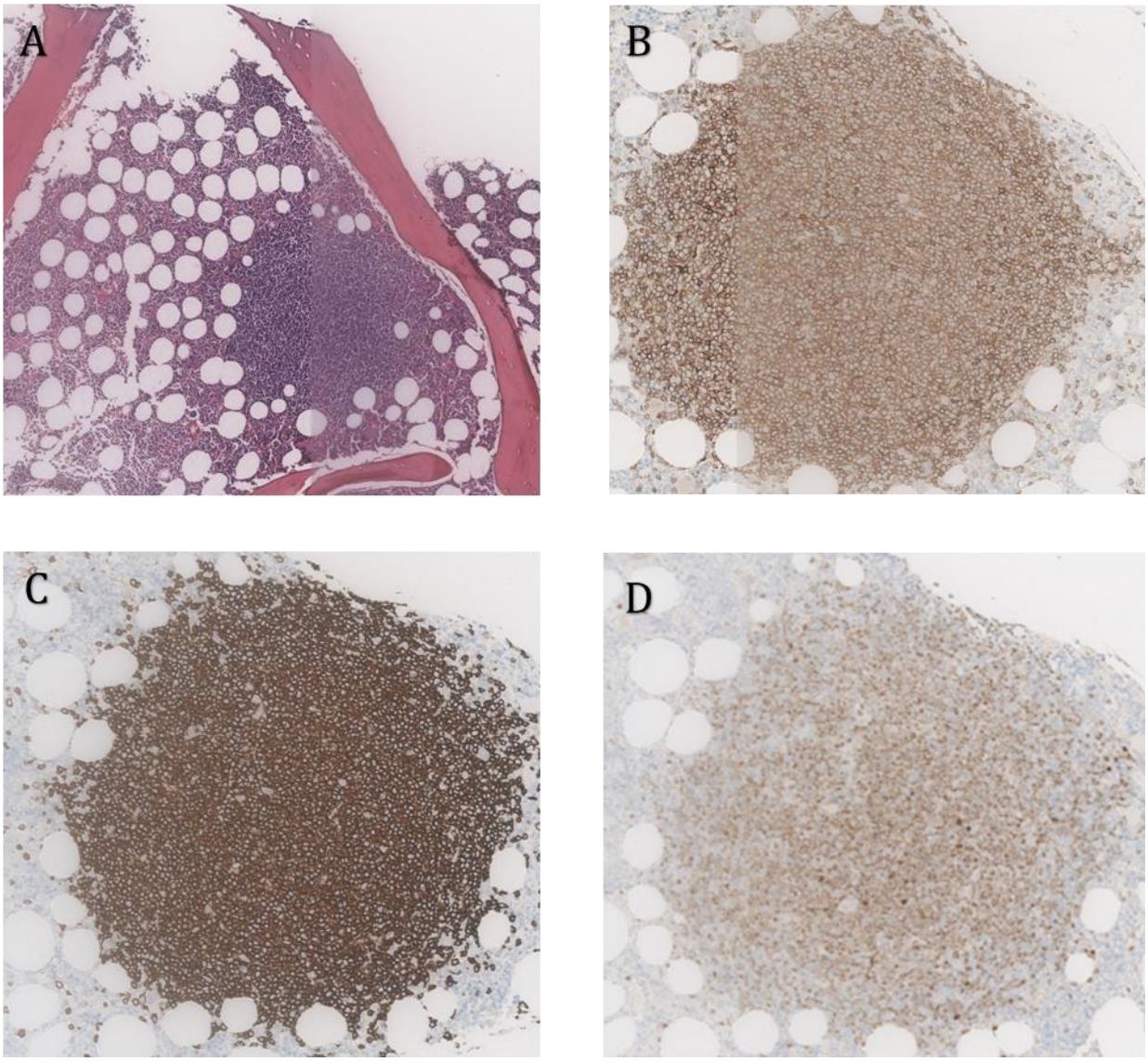

Figure 1: (A) focal infiltration of the marrow by lymphoma cells (Haematocylin & Eosin at low power field (magnification x20), (B) Immunohistochemistry for CD5 (magnification x40), (C) Immunohistochemistry for CD20 (magnification x40), (D) Immunohistochemistry for Cyclin D1 (magnification x40)

Discussion

Classical MCL typically presents with lymphadenopathy, extensive extranodal involvement, bone marrow infiltration, peripheral blood involvement, and hepatosplenomegaly. Common symptoms, known as B symptoms, include fever, weight loss, fatigue, night sweats, and chills. Conversely, leukemic non-nodal MCL is a separate subtype characterized by the absence of detectable lymphadenopathy despite peripheral blood, bone marrow, or splenic involvement[3]. Our patient presented with cervical lymphadenopathy and B symptoms, which are indicative of the classical type of MCL.

MCL is characterized by chromosomal translocation, t (11;14) (q13; q32), which occurs in over 95% of cases. This translocation fuses the cyclin D1 gene with the immunoglobulin heavy chain gene, resulting in overproduction of cyclin D1. This overexpression drives cancer cell growth and proliferation by disrupting the cell cycle, inducing epigenetic changes, and causing chromosomal instability. In cases without this translocation, alternative translocations involving CCND2 or CCND3 might be present, usually resulting in lower cyclin D1 expression. Interestingly, our case showed positive cyclin D1 immunohistochemistry despite the absence of the typical CCND1 rearrangement.

The immunophenotype of MCL typically involves the expression of pan-B cell markers, including CD19, CD20, CD79a, and PAX5, and aberrant expression of CD5[1,4,5]. Strong cyclin D1 expression and SOX-11 positivity, as detected by immunohistochemistry, are also characteristic of MCL. These markers are crucial for diagnosing MCL and differentiating it from other types of non-Hodgkin lymphomas, including Chronic Lymphocytic Leukaemia, Follicular Lymphoma, and Diffuse Large B-cell Lymphoma[6].

Cytogenetic evaluation to detect the t (11;14) (q13; q32) translocation, identifiable via karyotyping or FISH, is crucial for diagnosing MCL[6,7]. FISH studies usually detect CCND1/IGH rearrangements using dual-colour fusion (D-FISH) or, less commonly, break-apart probe sets. In our case, FISH studies were negative for the CCND1/IGH translocation. Peterson JF et al. reported a similar case with strong cyclin D1 positivity observed via immunohistochemistry despite the absence of CCND1/IGH rearrangement detected by FISH. This discrepancy was attributed to the cryptic nature of the genetic alteration, which evaded detection by standard FISH techniques due to the minimal size of the CCND1 gene segment inserted into the IGH locus[8]. Molecular investigations might include analysing somatic mutations in IGHV genes and/or using targeted DNA sequencing to identify somatic mutations when possible. Additionally, it is recommended to perform FISH analysis for TP53 or detect the 17p deletion. Mutations in the TP53, SMARCA4, NOTCH1/2, and CCND1 genes offer valuable prognostic insights. Among these, TP53 mutations, identified through DNA sequencing, are associated with the worst survival outcomes[6].

The treatment choice for individuals with MCL is determined by several factors, including the patient's age, performance status, comorbidities, and fitness level. For younger or physically fit patients, more aggressive combination therapies, such as rituximab and cytarabine, may be administered to combat the disease more effectively[2]. These treatments can help slow the progression of MCL and improve the patient's overall quality of life[6].

Conclusion

This case highlights the complexities involved in diagnosing and managing MCL, emphasizing the importance of a multidisciplinary approach tailored to individual patient characteristics and disease biology. Comprehensive genetic characterization is crucial in understanding the underlying molecular mechanisms, predicting disease behaviour, and guiding therapeutic decisions.

Declaration

Author(s) declares that no conflict of interest.

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Consent of patients and ethics

Consent for publication of this article has been provided by the patient

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