Case Report

DOI: 10.4274/haseki.galenos.2024.9567
Med Bull Haseki 2024;62:124-127

Blastoid Variant Mantle Cell Lymphoma with Amplified *IGH/CCND1* Fusion: A Unique Case and Current Literature Review

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Abstract

Mantle cell lymphoma (MCL) is a subtype of mature B-cell non-Hodgkin lymphoma (NHL). Most cases exhibit *CCDN1/IGH* translocation; however, reports indicate that amplification of the fusion gene is extremely rare. A 72-year-old male patient diagnosed with an MCL blastoid variant was referred to us. Amplified *CCDN1*(11q13)/*IGH*(14q32.3) fusion genes were observed in 75% of the interphase nuclei of the patient. We present the first case of blastoid variant MCL with multiple *IGH/CCND1* fusion signals by interphase fluorescence in situ hybridization. Our patient exhibited an aggressive course and passed away on the second day of treatment.

Keywords: Mantle cell lymphoma, *IGH/CCND1*, fusion, amplification, fluorescence in situ hybridization

Introduction

Mantle cell lymphoma (MCL) is a subtype of mature B-cell non-Hodgkin lymphoma (NHL), accounting for approximately 7% of adult NHL. Mantle cell lymphoma, which is mostly seen in older men, exhibits clinical and genetic heterogeneity (1). Mantle cell lymphoma tends to disseminate to the bone marrow, blood, lymphoid tissues, and extranodal sites, particularly the gastrointestinal tract (2). Morphologically, there are three types of MCL: classical, pleomorphic, and blastoid variants (1). Most cases carry t(11;14)(q13;q32)/*CCND1/IGH*, which juxtaposes the *IGH* locus with the *CCND1* gene, resulting in *CCND1* overexpression. Deregulation of *CCND1* expression increases the G1–S transition in the cell cycle and induces tumor development (3).

More than half of the cases with *IGH/CCND1* translocation have additional chromosomal rearrangements, particularly: del(1p), +3, del(6q), del(7q), +7, -8, del(9p), +12, del(13q), del(17p) +18, + mar (4). Moreover, MCL cases have shown abnormalities in the *TP53* and *ATM* genes (5).

We report a case of blastoid variant mantle cell leukemia with multiple *IGH/CCND1* fusion signals detected by interphase fluorescence in situ hybridization (FISH). To our knowledge, this is the first case showing amplification of the *IGH/CCND1* gene in blastoid variant mantle cell lymphoma.

Case Presentation

A 72-year-old male patient was diagnosed with bladder papillary urothelial carcinoma. A 2×2 cm lymphadenopathy was detected in the left supraclavicular area. The complete blood count showed leukocytosis (White blood cell 21.5×10^9/L; normal range 4.5-11×10^9/L) and anemia (Hemoglobin 10.6 g/dL; normal range 12-16 g/dL). A computed tomography scan of the abdomen revealed suggestive lymphoma, thickening of the terminal ileum wall, as well as paraaortic and mesenteric

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Received: 09.10.2023 **Accepted:** 03.03.2024

*Presented as an oral presentation at the 2nd National HematoOncoGenetics Congress, 4-7 May 2023, Bafra, KKTC.

lymphadenopathy. Only weight loss and constitutional type B symptoms were present, with no reports of fever or night sweats. The patient was referred to the hematology clinic. However, he initially refused all the recommended strategies; until a few weeks later, the patient consented to a colonoscopy and a biopsy at the suspicious tumor site. Pathology revealed a blastoid variant of the MCL in a biopsy of the right colon. Immunohistochemical evaluation showed that tumor cells were positive for CD20, CD5, BCL-2, and cyclin D1 in only 40% of cells. BCL-6 was positive and negative for SOX 11, LEF-1, CD10, CD3, and CD23 staining (Figure 1). The Ki-67 proliferation fraction was determined to be 80%, which is associated with a poor prognosis.

The patient, who was found to have bone marrow involvement on positron emission tomography and was evaluated as stage IV according to the Ann-Arbor staging system, was referred to our department of medical genetics. Fluorescence in situ hybridization analyses were performed using an *IGH/CCND1* plus translocation, dual-fusion probe (Cytocell, LPH 072) for *CCND1/IGH* rearrangements on the bone marrow aspirate sample. *CCND1*(11q13)/*IGH*(14q32.3) translocation and amplified fusion genes with three to six yellow signals were observed in 75% of the interphase nuclei (Figure 2A). Additional interphase nuclei FISH analysis was performed using an *MYC*(8q24) break-apart probe (Cytocell, LPH 010), *ATM*(11q22.3) (Cytocell, LPH 011), and TP53 (17p13.1) deletion probe (PrimeFISH, LS 17-003) (Figure 2B-D). They revealed a 23% heterozygous deletion in the *TP53* gene, a 100% homozygous deletion in the *ATM* gene, and no amplification or rearrangement in the *MYC* region. Chromosome analysis, which was performed using the G-banding technique on short-term (24 hours) cultured bone marrow cells, showed 47,XY,+mar [2]/46,XY [5]. The patient was planned to undergo R-CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) chemotherapy but died on the second day of rituximab treatment because of tumor lysis syndrome.

Discussion

Mantle cell lymphoma is caused by the abnormal proliferation of mature B cells. In the clinical course of the disease, the blood, bone marrow, and other systems, especially the gastrointestinal tract, might be involved (2). Both conventional cytogenetics and FISH analyses are commonly performed on patients. Our patient, who had gastrointestinal MCL involvement, underwent these analyses. *MYC* copy number changes and rearrangements are widely observed in aggressive variants of MCL and are associated with a poor prognosis. However, there was no rearrangement or copy number change in the *MYC* gene in our patient (6-9). In addition, *ATM* and/or *TP53* gene deletions are expected in these cases. *ATM* is a tumor suppressor gene, and its deletion is thought

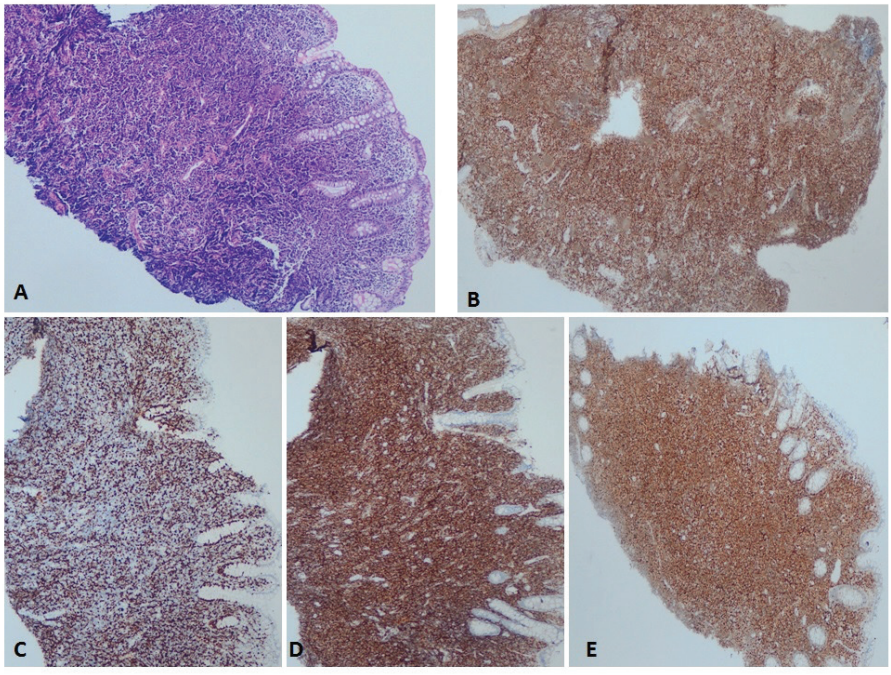

Figure 1. Morphology and immunocytochemistry of the right colon biopsy specimen: **A)** Hematoxylin&Eosin (H&E) staining and positive immunohistochemical stains of **B)** Cyclin D1, **C)** Ki-67, **D)** CD5, **E)** BCL-2, all of them are consistent with MCL (A-E, ×200 μm)
MCL: Mantle cell lymphoma

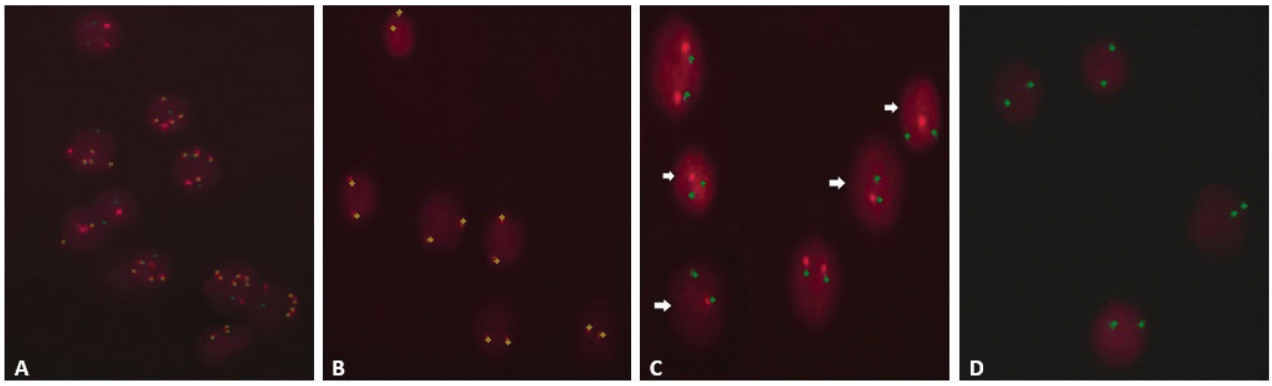

Figure 2. Fluorescence in situ hybridization (FISH) analysis. **A)** Using the *IGH/CCND1* plus translocation, dual-fusion probe in the bone marrow aspirate; the presence of the t(11;14)(q13;q32) and amplification of the *CCND1-IGH* fusion gene were observed. **B)** *MYC* FISH using the dual-color break-apart probe showed no amplification or rearrangement of the *MYC* gene. **C)** Heterozygous deletion with *TP53* probe was seen in a number of nuclei (indicated by arrows) with one red and two green signals. **D)** Homozygous deletion of the *ATM* gene was observed in all nuclei having solely green signals

to be effective in the onset and progression of the disease. Schaffner et al. (10) demonstrated that *ATM* gene deletion was found in 58% (7/12) of MCL patients. Similarly, *TP53* gene deletions are frequently observed in MCL cases and are associated with aggressive diseases. It was observed in 29 of 176 (16%) MCL patients that were unresponsive to intensive chemoimmunotherapy (9,10). We found a 23% heterozygous deletion in the *TP53* gene and a 100% homozygous deletion in the *ATM* gene in our patient. We believed that these changes in the patient could have contributed to his early death following the diagnosis.

To the best of our knowledge, this is the first report of amplification of the *IGH/CCND1* gene in the blastoid variant of mantle cell lymphoma. In the literature, five cases of *IGH/CCND1* fusion amplification have been presented. The diagnosis for them was one each of classical type MCL, pleomorphic type MCL, anaplastic multiple myeloma, and two cases of plasma cell leukemia (1,5-7,11).

The first case reported was a 58-year-old female patient with splenomegaly and lymphocytosis. She received an MCL diagnosis after splenectomy, and FISH analysis detected *IGH/CCND1* fusion amplification. The patient had a complex karyotype and a heterozygous deletion in the *TP53* gene region. The patient began treatment with chlorambucil and prednisolone, but died within 6 months, despite the average life expectancy of MCL cases being 2.5-4.5 years (5).

The second case was a 64-year-old male patient with bone pain, splenomegaly, and enlarged lymph nodes on the left side of his neck. He was diagnosed with plasma cell leukemia on bone marrow examination and had a complex karyotype and amplification of the *IGH/CCND1* fusion gene. He died very soon after the initiation of intensive chemotherapy treatment (6).

The third case was a 78-year-old male patient with night sweats, fatigue, dyspnea, and palpable masses in the groin and arm. Doctors diagnosed the patient with MCL, observing intense lymphoid cell infiltration in the bone marrow. The bone marrow cytogenetic examination detected a complex karyotype including t(11;14), and the FISH analysis detected *IGH/CCND1* fusion amplification in approximately 90% of the interphase cells. The patient also displayed monosomy 13 and *MYC* gene amplification. *TP53, ATM*, and *BCL2* gene deletion, rearrangement, and variation analyses were normal. Despite aggressive chemotherapy and radiotherapy, the patient deceased within approximately 15 months (1).

The fourth case was a middle-aged adult with dyspnea, bruising, anemia, and leukopenia. The patient's bone marrow was hypercellular, and 90% of the cells were composed of plasma cells. Her diagnosis was plasma cell leukemia. Fluorescence in situ hybridization analysis observed *CKS1B* (1q) amplification, heterozygous deletion of 13q, and *IGH/CCND1* fusion amplification, but conventional cytogenetic analysis failed. Although the patient received combination chemotherapy, she died within approximately 1 year (7).

The other case from the literature was a male patient with weight loss and low back and rib cage pain. The tomography revealed lytic lesions, and the bone marrow aspirate revealed 46.4% pleomorphic plasma cells, leading to the diagnosis of multiple myeloma. Conventional cytogenetics resulted in normal. Fluorescence in situ hybridization analysis revealed *IGH/CCND1* fusion amplification, *CKS1B* amplification, 13q deletion, and *TP53* gene deletion. This case also had a poor clinical course (11).

Here we report the sixth patient with *IGH/CCND1* fusion amplification reported in the literature and the third one

with mantle cell lymphoma. To the best of our knowledge, this is the first case of blastoid variant MCL with an amplified *IGH/CCND1* fusion gene. It is important to present cases with rare molecular cytogenetic abnormalities to enhance our understanding of their possible effects on prognosis and contribute to the literature.

Ethics

Informed Consent: Informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: E.G., H.H.E., A.T., Concept: E.G., Design: E.G., Data Collection or Processing: E.G., H.H.E., A.T., Analysis or Interpretation: E.G., S.S., Literature Search: E.G., S.S., Writing: E.G., S.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

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