Int J Clin Exp Pathol 2014;7(4):1800-1804
www.ijcep.com /ISSN:1936-2625/IJCEP1401072

Case Report

Therapy-related B lymphoblastic leukemia with t(4;11)(q21;q23)/*AF4-MLL* in a patient with mantle cell lymphoma after recent aggressive chemotherapy - a unique case report

Stephanie L Holdener[1], Lacey Harrington[1], Johnny Nguyen[1], Pedro Horna[2], Elizabeth Sagatys[2], Bijal Shah[3], Ling Zhang[2]

[1]Department of Pathology, University of South Florida Morsani College of Medicine, Tampa, FL, USA; Departments of [2]Hematopathology and Laboratory Medicine, [3]Hematological Malignancies, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

Received January 20, 2014; Accepted February 4, 2014; Epub March 15, 2014; Published April 1, 2014

Abstract: Mantle cell lymphoma (MCL) is a mature B-cell lymphoma associated with the hallmark translocation t(11;14)(q13;32), which involves the cyclin D1 (*CCND1*) and immunoglobin heavy chain (*IgH)* genes. It may transform to a more aggressive blastoid or pleomorphic variant, with or without acquisition of chromosomal abnormalities. MCL could also present with a leukemic phase with marked lymphocytosis. A literature search did not reveal any prior reports of MCL transforming to or followed by a B-cell lymphoblastic leukemia (B-ALL).

Keywords: Mantle, lymphoma, therapy, transformation, variant

Clinical history

A 62-year old man with a past medical history of prostatic adenocarcinoma (diagnosed in August 2010 and is status post radical prostatectomy, without additional radiation or chemotherapy, prostatic carcinoma Gleason score 7, T2c NX MX), splenectomy after trauma sustained at the age of 24, presented with general lymphadenopathy while being treated for a dental infection in December 2011. A biopsy taken from a left axillary lymph node was performed by an outside facility immediately after a CT scan showed extensive disease involving multiple peripheral and mediastinal lymph nodes (0.5 to 2.0 cm in size). The biopsy revealed mantle cell lymphoma (MCL), which was confirmed with FISH for t(11;14)/*IGH-CCND1*. The patient was transferred to our institution for further management. A complete blood count (CBC) showed a white blood cell count (WBC) of 10.24 × 10^9/L with mild eosinophilia, a red blood cell count of 4.29 × 10^9/L, hemoglobin level of 12.3 g/L, and platelet count of 482 × 10^9/L. There was no atypical lymphocytosis. Lymphocytes comprised 26% of the differential count, and a staging bone marrow biopsy performed showed 80% cellularity with an atypical lymphoid infiltrate arranged in aggregates, occupying nearly 40% of the cellularity (**Figure 1A**). The bone marrow aspirate was partially hemodilute, composed of approximately 10% atypical small lymphoid cells that had irregular nuclear contours, dispersed chromatin, and scant cytoplasm (**Figure 1B**). There was no notable morphologic dysplasia in all three hematopoietic lineages. The corresponding flow cytometry performed demonstrated a small population of clonal lymphoid cells (4% of the total cellularity) expressing CD19, CD20 (bright), CD5, and FMC-7, with lambda light chain restriction (**Figure 1C**). Additionally, CD23 and CD10 tested negative. Although the karyotype was normal (46,XY[20]), fluorescence in-situ hybridization (FISH) analysis indicated 6.0% of the nuclei were positive for the *CCND1/IGH* dual fusion. A chemotherapy regimen consisting of fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone plus rituximab (R-HyperCVAD) was administered for

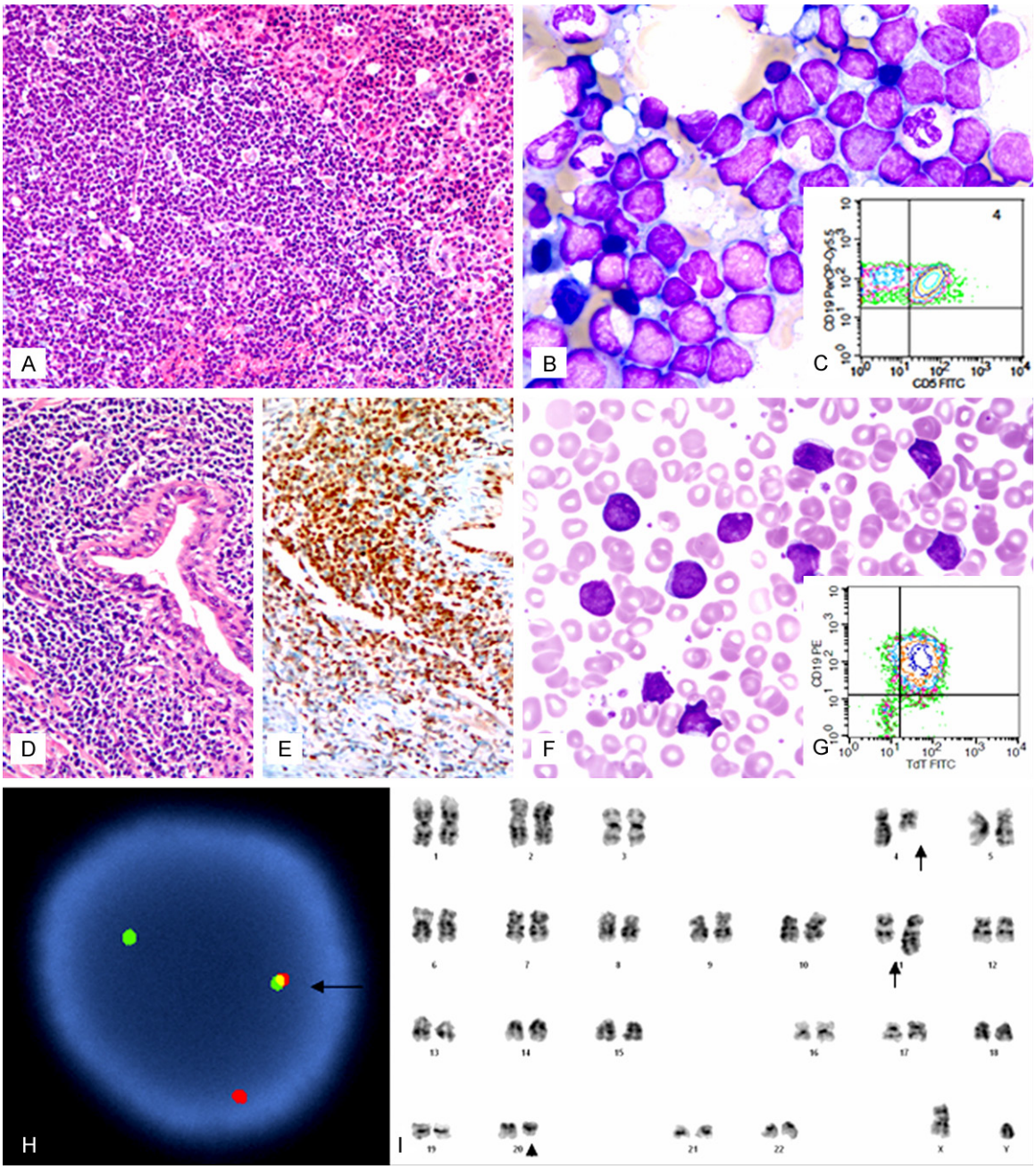

Figure 1. (A) The MCL staging bone marrow biopsy showed extensive involvement by an atypical lymphoid infiltrate occupying nearly 40% of the cellularity. (B) The bone marrow aspirate (partially hemodilute) was composed of approximately 10% atypical small lymphoid cells with irregular nuclear contours, dispersed chromatin, and scant cytoplasm. (C) A flow cytometry analysis revealed a small population of clonal lymphoid cells (4% total cellularity), expressing CD19 and CD5, which was consistent with MCL. (D) A retrospective immunohistochemical staining of prostatic tissue exhibited perivascular and stromal atypical lymphoid aggregates (E), which stained positive for PAX-5. (F) A post-MCL peripheral blood smear collected two months later showed atypical lymphoid cells with a high nuclear to cytoplasmic ratio, immature/blastoid chromatin, and prominent nucleoli. (G) Flow cytometry indicated a population of immature B-cell precursors expressing CD19 and TdT markers suggestive of B-lymphoblastic leukemia (B-ALL). (H) A FISH study demonstrating 72% of nuclei positive for the *MLL* gene rearrangement along with (I) the karyotype of 46,XY, t(4;11)(q21;q23), del(20)(q11.2)[13]/46,XY[2], further confirming a diagnosis of B-ALL.

6 cycles. A restaging bone marrow biopsy indicated successful clearance of MCL with a cellularity of 50%, and normal trilineage hematopoiesis. Karyotyping, FISH analysis, immuno-

phenotying and molecular studies were negative for residual MCL. A PET/CT study failed to show areas of increased uptake. The patient was put on a maintenance dose of rituximab every two months (three cycles) until December 2012.

A follow up flow cytometry study performed on his peripheral blood sample in November of 2012 showed no evidence of circulating residual lymphoma. A WBC count was unremarkable (2.41×10^9/L) and had a normal morphology. No blasts were noted. Two months later, however, his WBC increased significantly to 141.29×10^9/L, with 8% of them being atypical lymphoid cells with a high nuclear to cytoplasmic ratio, immature/blastoid chromatin, and prominent nucleoli (**Figure 1F**). A prompt flow cytometry study yielded immature B-cell precursors expressing CD19, CD22 (cytoplasmic), HLA-DR, CD38, CD34 and TdT (**Figure 1G**). They were virtually negative for CD5, CD10, CD11c, CD103, CD20, and kappa and lambda light chains. A subsequent bone marrow biopsy confirmed sheets of blasts occupying 85% of the cellularity. Karyotyping showed 46,XY, t(4;11)(q21;q23), del(20)(q11.2)[13]/46,XY[2] (**Figure 1I**). A FISH study showed 72.0% of the nuclei to be positive for the *MLL* gene rearrangement (**Figure 1H**), and 86% positivity for deletion of 20q but no other abnormal signals including *BCR-ABL*, *IGH-CCDN1*, deletion of 5q or monosomy 5, deletion of 7q or monosomy 7 and trisomy 8. A therapy-related ALL (t-ALL) was considered, for which he was started on a chemotherapy regimen of ifosfamide, etoposide, cytarabine, and methotrexate (IVAM) in February 2013. He was given two additional doses of intrathecal methotrexate and cytarabine in March 2013. The patient is currently in remission, and is preparing for an allogeneic hematopoietic stem cell transplant.

Interestingly, a retrospective review of the clinical history showed the patient had regional lymphadenopathy when he was initially diagnosed with prostatic adenocarcinoma. The regional ymph nodes were not biopsied and examined at the time. Additional immuohistochemical stains performed on the sections of prostatic tissue demonstrated perivascular and stromal atypical lymphoid aggregates (**Figure 1D**) (comprising less than 3% of the total tissue volume), which stained positive for CD20, PAX-5 and BCL-1 (**Figure 1E**, PAX5). This immunoprofile suggested an indolent MCL dating back to August 2010.

Discussion

Mantle cell lymphoma (MCL) is a B-cell neoplasm containing small lymphoid cells that arise from naïve B-cells, and develop in the inner mantle zone of the secondary lymphoid follicle. It accounts for 3-10% of non-Hodgkin lymphoma, is more common in males than females, and is usually diagnosed at an advanced stage. Extranodal disease is common especially in the blood, spleen, bone marrow, Waldeyer's ring, and the gastrointestinal tract [1]. MCL can be characterized by the immunophenotype CD5(+), CD20(+), CD10(-), BCL-6(-), lambda light chain restriction, and the characteristic translocation t(11;14)(q13;32)/*IGH-CCND1* [1, 2]. Secondary genetic alterations have been well documented in MCL, including gain of 3q26, 7p21, 8q24 *MYC* as well as trisomy 12 [2, 3]. Also, dysregulation of INK4a/CDK4/RB1 and ARF/MDM2/p53 cell cycle pathways via mutation or amplification have been implicated in the etiology of classic MCL and more aggressive forms such as the blastoid subtype [4]. A chromosmal aberration involving loss of 11q21-q23, containing the *MLL* gene, but not *MLL* gene rearrangement, was found in a subset of MCL [5]. The loss of 11q21-q23 was not reportedly associated with transformation to lymphoblastic leukemia/lymphoma. The blastic variant of MCL may display a "lymphoblastic" morphology resembling lymphoblastic leukemia. This MCL variant is frequently refractory to chemotherapy [6, 7]. However, the two can be distinguished by relatively preserved blood counts, denser chromatin patterns, light chain clonality and the lack of the immature phenotype (TdT, CD34) in conventional MCL compared to lymphoblastic leukemias [6, 8], in conjunction with cytogenetic studies.

B-lymphoblastic leukemia (B-ALL) comprises about 80% to 85% of all acute lymphoblastic leukemia, and occurs mostly in young children [9]. Therapy-related acute lymphoblastic leukemia (t-ALL) has been reported, accounting for approximately 12% of all therapy-related acute leukemias and 1.2% to 4% of adult acute lymphoblastic leukemia, with or without the *MLL* gene rearrangement [10, 11]. The origins of the primary malignancies mainly included breast, prostate, lung, cervical, thyroid, and colorectal, and hematological such as plasma cell myeloma and some lymphomas [10-12]. However, mantle cell lymphoma has not been reported.

The arrangement of the *MLL* gene, which encodes a histone methyltransferase, is commonly noted in many therapy-related leukemias, and has shown to be associated with prior topoisomerase II inhibitor therapy [13]. The *MLL* gene rearrangement is also one of the key steps triggering t-ALL [10, 12]. A pro-B lymphoblastic leukemia phenotype (CD10 negative) was the most frequently seen in *MLL* gene related t-ALL [10], as was seen in our case. The latency period of 11q23/*MLL* gene related t-ALL development varies significantly. According to a large scale retrospective study, 44 adults of 457 with B-ALL had prior malignancies. Thirty out of 44 of the patients received cytotoxic therapies and presented with a shorter latency period of 36 months than those without therapy (144 months) [12]. The t(4;11)(q21;q23) or *MLL* gene aberration was seen in patients with t-ALL that received both the topoisomerase II inhibitors and alkylating agents and was associated with a worse clinical outcome [12]. We performed a retrospective FISH study (*MLL* gene rearrangement) on all available in-house bone marrow paraffin sections that had a diagnosis of MCL, MCL in remission, and the first evidence of B-ALL. The results showed an *MLL* gene rearrangement was only detected in the BM with a diagnosis of B-ALL, but not in MCL at the time of diagnosis or in MCL in remission. Considering the fact that the patient was treated with HyperCVAD-R (an alkylating agent, mitotic inhibitor, DNA intercalator, anti-inflammatory steroid, and an antimetabolite) this could help account for his development of t-ALL after acquisition of the *MLL* gene.

It is known that deletion of 20q or del(20q) is often associated with myeloid neoplasms [14], however, its significance in non-myeloid disorders has yet to be defined. There are only two case studies reported with del(20q) in B-ALL, but both Philadelphia chromosomal abnormalities were positive [15]. The exact role of the deletion of 20q in the same B-ALL cells harboring t(4;11)/AF4-MLL is unclear in this setting and has not been reported.

Conclusion

In closing, we present an unusual case of t-ALL with an *MLL* gene acquisition and deletion of 20q11.2 that developed in a patient with a history of MCL and prostatic adenocarcinoma. This very unique clinical presentation warrants a large scale, multi-institutional study to better understand the molecular mechanisms of secondary hematopoietic malignancies in MCL.

Acknowledgements

We appreciate Brenda Barrow's assistance in editing the manuscript and Peter Papenhausen and Carla Kelly from Integrated Oncology - LabCorp, who provided the karyotyping map and FISH picture. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

Address correspondence to: Dr. Ling Zhang, Department of Hematopathology and Laboratory Medicine, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Dr., Tampa, FL 33612, USA. Tel: 813-745-2852; E-mail: ling.zhang@moffitt.org

References

[1] Vose JM. Mantle cell lymphoma: 2012 update on diagnosis, risk-stratification, and clinical management. Am J Hematol 2012; 87: 604-609.

[2] Swerdllow S, Campo E, Seto M and Mueller-Hermelink H. Mantle cell lymphoma. WHO classification of tumours of haematopoietic and lymphoid tissues. France: IARC Press; 2008. pp: 229-232.

[3] Bierman P, Harris N, Armitage J and Appelbaum F. Non-Hodgkin Lymphomas. Cecil Textbook of Internal Medicine. Philadelphia, PA: Saunders; 2008. pp: 1390-1397.

[4] Jares P, Colomer D and Campo E. Molecular pathogenesis of mantle cell lymphoma. J Clin Invest 2012; 122: 3416-3423.

[5] Rubio-Moscardo F, Climent J, Siebert R, Piris MA, Martin-Subero JI, Nielander I, Garcia-Conde J, Dyer MJ, Terol MJ, Pinkel D and Martinez-Climent JA. Mantle-cell lymphoma genotypes identified with CGH to BAC microarrays define a leukemic subgroup of disease and predict patient outcome. Blood 2005; 105: 4445-4454.

[6] Rutledge N, Casas T and Gentry JF. Mantle Cell Leukemia, Blastoid Variant. Lab Medicine 2005; 36: 168-173.

[7] Bernard M, Gressin R, Lefrere F, Drenou B, Branger B, Caulet-Maugendre S, Tass P, Brous-

se N, Valensi F, Milpied N, Voilat L, Sadoun A, Ghandour C, Hunault M, Leloup R, Mannone L, Hermine O and Lamy T. Blastic variant of mantle cell lymphoma: a rare but highly aggressive subtype. Leukemia 2001; 15: 1785-1791.

[8] Wong KF, Chan JK, So JC and Yu PH. Mantle cell lymphoma in leukemic phase: characterization of its broad cytologic spectrum with emphasis on the importance of distinction from other chronic lymphoproliferative disorders. Cancer 1999; 86: 850-857.

[9] Pui CH, Robison LL and Look AT. Acute lymphoblastic leukaemia. Lancet 2008; 371: 1030-1043.

[10] Ishizawa S, Slovak ML, Popplewell L, Bedell V, Wrede JE, Carter NH, Snyder DS and Arber DA. High frequency of pro-B acute lymphoblastic leukemia in adults with secondary leukemia with 11q23 abnormalities. Leukemia 2003; 17: 1091-1095.

[11] Chen W, Wang E, Lu Y, Gaal KK and Huang Q. Therapy-related acute lymphoblastic leukemia without 11q23 abnormality: report of six cases and a literature review. Am J Clin Pathol 2010; 133: 75-82.

[12] Tang G, Zuo Z, Thomas DA, Lin P, Liu D, Hu Y, Kantarjian HM, Bueso-Ramos C, Medeiros LJ and Wang SA. Precursor B-acute lymphoblastic leukemia occurring in patients with a history of prior malignancies: is it therapy-related? Haematologica 2012; 97: 919-925.

[13] Mauritzson N, Albin M, Rylander L, Billstrom R, Ahlgren T, Mikoczy Z, Bjork J, Stromberg U, Nilsson PG, Mitelman F, Hagmar L and Johansson B. Pooled analysis of clinical and cytogenetic features in treatment-related and de novo adult acute myeloid leukemia and myelodysplastic syndromes based on a consecutive series of 761 patients analyzed 1976-1993 and on 5098 unselected cases reported in the literature 1974-2001. Leukemia 2002; 16: 2366-2378.

[14] Kurtin PJ, Dewald GW, Shields DJ and Hanson CA. Hematologic disorders associated with deletions of chromosome 20q: a clinicopathologic study of 107 patients. Am J Clin Pathol 1996; 106: 680-688.

[15] Hollings PE, Benjes SM, Rosman I and Fitzgerald PH. Deletion 20q in association with Philadelphia chromosome positive acute lymphoblastic leukemia. A report of two cases. Cancer Genet Cytogenet 1995; 79: 32-35.