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

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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 \times 10^9/L with mild eosinophilia, a red blood cell count of 4.29 \times 10^9/L, hemoglobin level of 12.3 g/L, and platelet count of 482 \times 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...
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-
phenotyping 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 x 10^9/L) and had a normal morphology. No blasts were noted. Two months later, however, his WBC increased significantly to 141.29 x 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 cellularularity. Karyotyping showed 46,XY, t(4;11) (q21;q23), del(20)(q11.2)[13]/46,XY[2] (Figure 1H). A FISH study showed 72.0% of the nuclei to be positive for the MLL gene rearrangement (Figure 1I), and 86% positivity for deletion of 20q but no other abnormal signals including BCR-ABL, IGH-CCND1, 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 lymph nodes were not biopsied and examined at the time. Additional immunochemical 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 chromosomal 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.
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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.

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

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