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Article / Clinical Case Report

High-grade B-Cell lymphoma with *MYC* and *BCL6* rearrangements associated with Richter transformation of chronic lymphocytic leukemia

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ABSTRACT

Richter transformation (RT), or Richter syndrome, is defined as the transformation of chronic lymphocytic leukemia (CLL) to an aggressive B-cell lymphoma. The vast majority, up to 99%, transform into diffuse large B-cell lymphoma (DLBCL), with a small subset (<1%) becoming classical Hodgkin lymphoma. Approximately half of RT cases progress through a pathway involving dysregulation of C-MYC. High-grade B-cell lymphoma (HGBL) is a recent diagnostic category of aggressive B-cell lymphomas set forth in the updated 2017 WHO Classification of Hematopoietic and Lymphoid Tissues. HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements, formerly "double-hit" and "triple-hit" lymphomas, comprise the majority of HGBL cases. Patients with HGBL have a worse prognosis than those with diffuse large B-cell lymphoma. We present a case of RT with rearrangements of *MYC* and *BCL6*. To our knowledge, there are no reported cases of RT with a "double-hit" lymphoma genotype.

Keywords
Leukemia, Lymphocytic, Chronic, B-cell; Lymphoma, Non-Hodgkin; Lymphoma, Large B-cell, Diffuse; Cytogenetics

CASE REPORT

A 59-year-old man with a 20-year history of CLL presented with progressive shortness of breath, weight loss, and a rapidly enlarging supraclavicular lymph node. Prior therapies included fludarabine, rituximab, bendamustine, and ibrutinib. Though the CLL was never genetically characterized by FISH studies, there was a normal karyotype 3 years previously. At presentation, he had a mild microcytic anemia (HGB 11.4 g/dL; reference range [RR], 13.8-17.3 g/dL; MCV 79 fL; RR, 81-95 fL), normal white blood cell count (WBC 5,800/mL; RR, 4,000-10,400/mL), normal absolute lymphocyte count (ALC 2,090/mL; RR, 1,090-3,300/mL), and thrombocytopenia (PLT 107,000/mL; RR, 141,000-320,000/mL). LDH was elevated at 1,850 U/L (RR, 313-618 U/L). Imaging showed a large mediastinal mass with compression of the left atrium and pulmonary arteries. An excisional biopsy of the supraclavicular lymph node showed effacement of the normal nodal architecture by sheets of intermediate to large atypical lymphocytes with irregular nuclear contours and prominent nucleoli (Figure 1A). Numerous mitotic figures were present. The proliferation index, assessed by KI-67 (MIB-1), was increased at 60-70% (Figure 1B).

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Flow cytometry of the lymph node detected a lambda-restricted clonal CD5-positive B-cell population also positive for CD20(dim) and CD23(dim), and negative for CD10 and FMC7 (Figure 2).

This immunophenotype was similar to those seen in the patient's multiple previous specimens, including lymph nodes, bone marrow, and peripheral blood over the prior 20 years. In the current study, a significant component of large cells was seen by light scatter criteria.

Cytogenetic studies revealed an abnormal karyotype with a translocation between the long

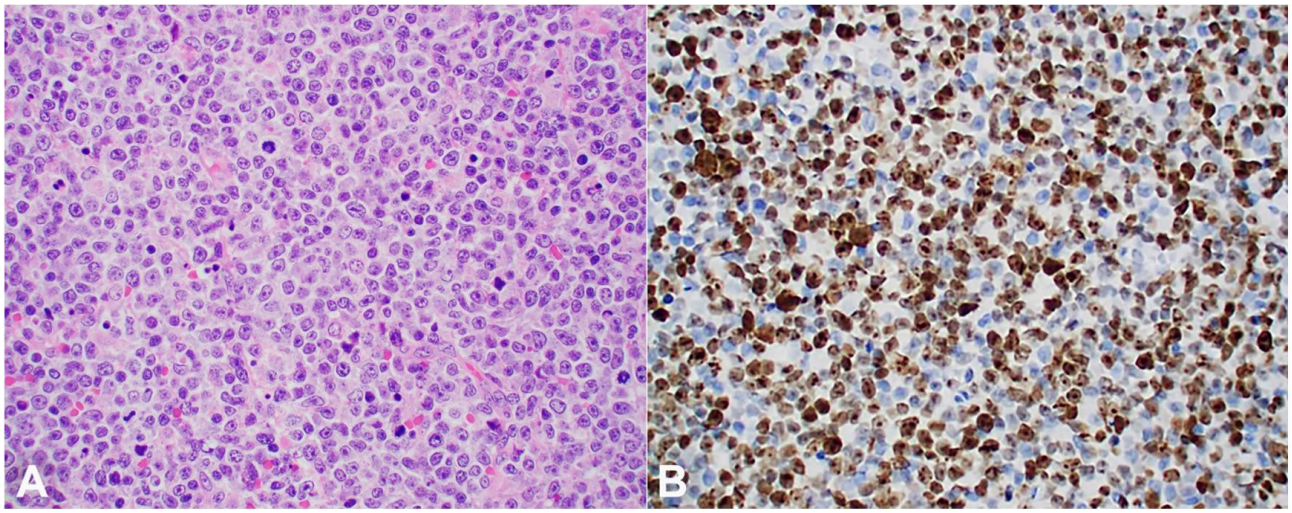

Figure 1. A – Photomicrograph of the supraclavicular lymph node showing sheets of intermediate-sized cells with prominent mitoses (H&E, 40X); **B –** Ki67 (MIB1) immunohistochemical stain, showing an estimated 60-70% proliferation rate (40X).

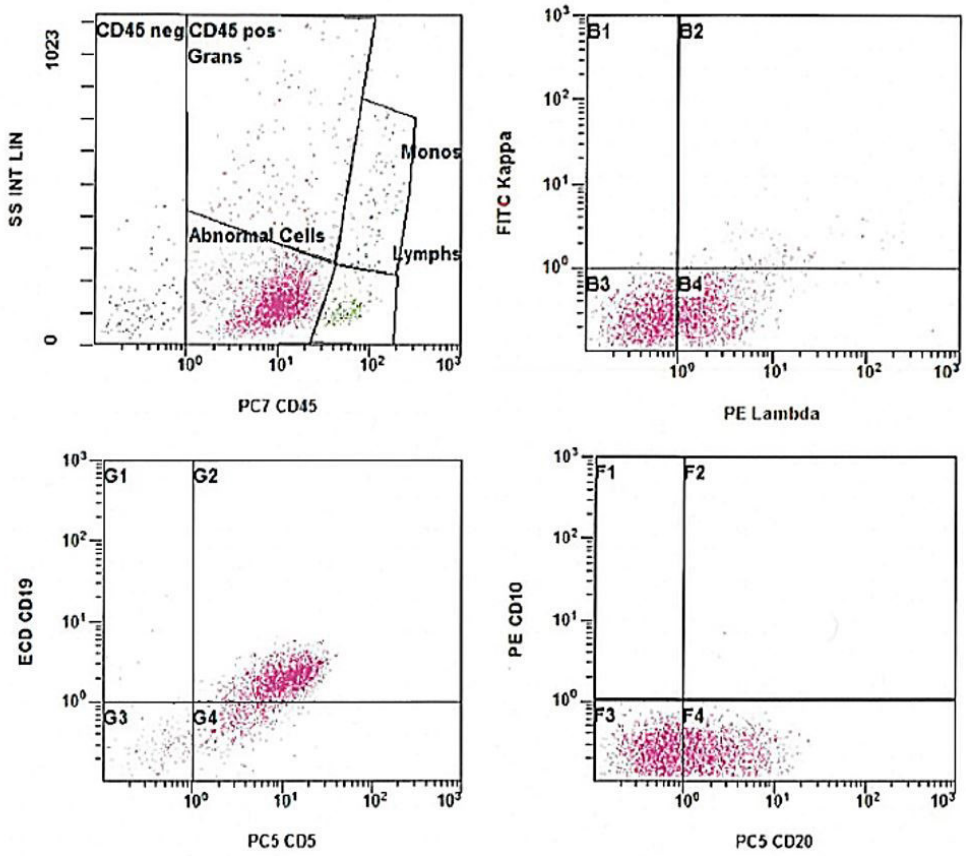

Figure 2. Flow cytometry of the lymph node, showing a CD19+ CD5+ CD10- lambda-restricted B-cell population. CD45 was aberrantly decreased. (SS: Side scatter; PE: Phycoerythrin; PC7: Phycoerythrin cyanin 7; PC5: Phycoerythrin cyanin 5; ECD: Electron coupled dye; B1-4, G1-4, F1-4: Plot quadrants).

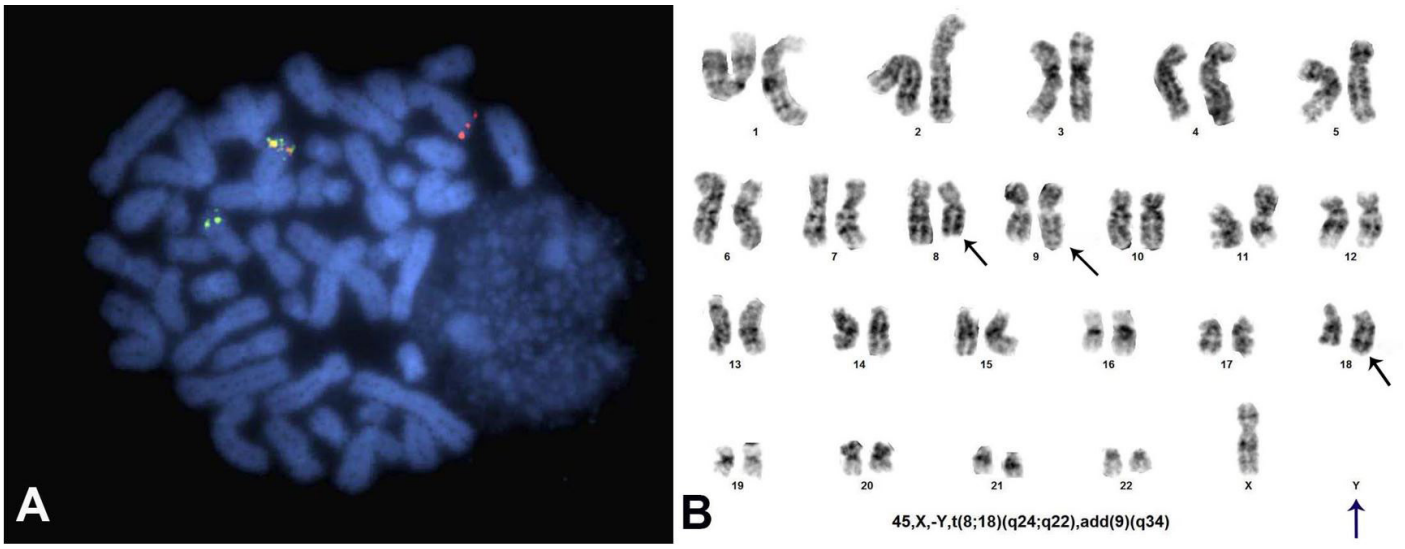

Figure 3. A – MYC break apart FISH demonstrating rearrangement of the MYC locus (Yellow: Intact MYC signal; Red, Green: Broken MYC signal); **B –** Conventional karyotype (Arrows indicate abnormal chromosomes listed in the ISCN nomenclature).

arms of chromosomes 8 and 18, additional material on the long arm of chromosome 9, and loss of the Y chromosome in 8 cells. A normal male karyotype was identified in 2 cells. There was an insufficient number of dividing cells for a 20-cell study. Fluorescence in situ hybridization (FISH) revealed a *MYC* gene rearrangement in 70-80% of cells and a *BCL6* gene rearrangement in 81% (Figure 3). FISH for *BCL2* gene rearrangement was negative. Clonal immunoglobulin gene rearrangements were detected by molecular analysis, but were different than the previous CLL clone.

The patient was treated with 3 cycles of R-CHOP, and after 2 months imaging showed progression of disease. He was started on R-ICE and underwent stem cell transplantation with successful engraftment. The disease continued to progress with involvement of the CNS and ultimately the patient developed respiratory failure. He was placed on hospice and succumbed to his illness, roughly 9 months after the initial diagnosis of transformation.

DISCUSSION

HGBL comprises a group of aggressive, mature B-cell lymphomas that can be further categorized as either "High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements" or "High-grade B-cell lymphoma, NOS."[1] Most cases belong in the former category, and were previously referred to as "double-" or "triple-hit" lymphomas (HGBL-DH). Prior to the 2016 revision to the WHO Classification of Hematopoietic and Lymphoid Tissues, these malignancies were classified as "B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma." These lymphomas typically occur in elderly patients and present at an advanced stage. About half have morphologic features typical of diffuse large B-cell lymphoma (DLBCL), while the other half have either morphologic features typical of Burkitt lymphoma or overlapping features of both. Thus, it is now recommended to do cytogenetic or molecular studies on all DLBCL, NOS cases to look for abnormalities of *MYC, BCL2,* and *BCL6*.[2]

Within HGBL-DH, which by definition have a *MYC* rearrangement, *BCL2* rearrangements are much more common than *BCL6*. One study found that out of 326 HGBL-DHs, 62% had rearrangements of *MYC* and *BCL2*, 16% had *MYC, BCL2* and *BCL6*, and 8% *MYC* and *BCL6*.[3] It is thought that HGBL-DH with *MYC/BCL2* has a poorer prognosis than those with *MYC/BCL6*.[4,5]

Richter transformation (RT) is the development of an aggressive non-Hodgkin lymphoma in the setting of underlying chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The onset of RT is heralded by sudden clinical deterioration, a marked increase in lymphadenopathy, splenomegaly, and worsening "B" symptoms such as fever, night sweats,

and weight loss. Risk factors for the development of RT remain poorly defined. However, several clinical features have been associated with RT including elevated serum lactate dehydrogenase, progressive lymphadenopathy, "B" symptoms, monoclonal gammopathy, and extranodal involvement.[6] Additionally, one study suggested lymph nodes >3 cm, absence of del13q14, CD38 expression and usage of *IGHV4-39* as additional risk factors.[7] Biopsy of a suspicious transformation site, in our case a rapidly enlarging lymph node, is required to establish the diagnosis.

Up to 99% of RT cases are those that result in diffuse large B-cell lymphoma (DLBCL), with a small subset (<1%) becoming classical Hodgkin lymphoma. From a molecular standpoint, RT may develop as a clone identical to the pre-existing CLL clone, evolve from a bi-clonal phenotype, or arise as an independent, secondary lymphoma.[8] The former two scenarios likely represent a complex, multistep process leading to the replication of a malignant clone of germinal or post-germinal B-cell origin manifesting as aggressive lymphoma. The molecular profile of RT-DLBCL is vastly different than that of de novo DLBCL.[9] One study using whole exome sequencing and copy number analysis found, on average, CLL acquires approximately 20 new genetic lesions during the transformation process including mutations of TP53, NOTCH1, INK4a/ARF, and CDKN2A/2B.[10,11] About 20% of RT cases are not clonally related to the original leukemia.[12]

Historically, RT has been associated with a dismal prognosis, with median survival reported between five to eight months from the time of diagnosis.[11] The most significant prognostic indicator in RT is clonal relation, with cases that are clonally unrelated having a better prognosis in general (median survival 5 years vs. 8-16 months).[9] Amplification and/or overexpression of *c-MYC* is associated with a particularly poor prognosis, even in the absence of translocation to an immunoglobulin locus such as IgH.[13,14] The overall response rate to chemotherapeutic regimens has been shown to be 39%, with 12% demonstrating a complete response.[15]

There have been differing study outcomes regarding the prognostic significance of HGBL-DH *MYC/BCL6*, with studies reporting both better and worse clinical outcomes.[5,16,17] Nonetheless, patients with HGBL are candidates for more aggressive chemotherapy regimens given high rates of relapse and poor survival following treatment with standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).[18] Autologous and allogeneic hematopoietic stem cell transplants have been explored as therapeutic options, showing modest benefit in patients with chemosensitive disease.[15]

In summary, our case represents a Richter transformation to high-grade B-cell lymphoma with *MYC* and *BCL6* rearrangements. The immunophenotype of the aggressive lymphoma was nearly identical to the pre-existing CLL; however, molecular studies did not identify a clonal relation.

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This manuscript is in accordance with our institution's ethics and research committee guidelines.

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