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Diffuse Large B-cell Lymphoma with *BCL6*::*MYC* Translocation due to a Rare t(3;8)(q27;q24) – Literature Review with Prognostic Data

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Case Report
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Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma. It comprises a heterogeneous group of diseases that varies in morphology, immunophenotype and molecular features. Evaluation of prognostic factors is important in determining the risk category of patients newly diagnosed with DLBCL. Analysis of *MYC*, *BCL2* and *BCL6* gene rearrangements is essential in identifying high-risk patients. Lymphomas with *MYC* and *BCL2* and/or *BCL6* gene rearrangements are known as high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements and are associated with a poor clinical outcome. We report a rare t(3;8) *BCL6*::*MYC* gene rearrangement in a DLBCL patient and include survival information in these subsets of patients. This case also underscores the clinical utility of metaphase FISH in identifying such rare abnormalities which are indistinguishable by the interphase FISH assay using breakapart FISH probes.

Keywords: B-Cell Lymphoma; *BCL6* Gene; Disease; Analysis; FISH

Abbreviations

DLBCL: B-Cell Lymphoma; THL: Triple-Hit Lymphoma; DHL: Double-Hit Lymphoma; FISH: Fluorescence in Situ Hybridization.

Introduction

Diffuse large B-cell lymphoma (DLBCL) comprises a spectrum of diseases with varying morphology, immunophenotype, and molecular characteristics. Analysis of *MYC*, *BCL2* and *BCL6* gene rearrangements is the main method for identifying the aggressive and newly dubbed high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement per the most recent updated terminology from both the World Health Organization and the International Consensus Classification groups [1,2], previously known as double-hit lymphoma (DHL) or triple-hit lymphoma (THL). These high-grade B-cell lymphoma rearrangements confer a worse overall outcome with aggressive disease requiring intensive treatment regimens [3,4]. The *MYC*, *BCL2*, and *BCL6* genes often are seen rearranged with immunoglobulin genes with the typical rearrangements easily recognizable on conventional cytogenetic testing with G-banding.

Fluorescence in situ hybridization (FISH) with locus specific probes is a second and more rapid method to test for the rearrangements seen with these three oncogenes; however, not all cases exhibit classic rearrangements. t(3;8) is a rare rearrangement seen in DLBCL which functions as a "pseudo-double-hit", equivalent to a single-hit *MYC*-activating rearrangement [5-7].

Herein, we report the case of a patient diagnosed with DLBCL with this rare t(3;8) *BCL6*::*MYC* gene rearrangement. The utility of metaphase FISH is further described in identifying the cryptic translocation not seen in interphase FISH. A literature review of similar t(3;8) rearrangements is provided with survival data and comparison to the case presented here.

Case Report

A 65-year-old female presented to her primary care provider with increasing abdominal pain, diarrhea, nausea, and weight loss. Upon evaluation, a CT was obtained and showed an irregular left abdominopelvic mass (24.5 cm), involving the peritoneum, omentum, small bowel, and splenic flexure of the colon. Her serum LDH level was elevated at 1,154 U/L (100-210 U/L). The remainder of her labs are significant for anemia with a hemoglobin of 10.9 g/dL (12.0-15.0 g/dL), platelet count of 580 K/µL (150-400 K/µL), mild leukocytosis with a white blood cell count of 13.4 K/µL (4.5-11.1 K/µL), and neutrophilic predominance.

A core needle biopsy of the abdominal mass (Figure 1) was performed and showed DLBCL, germinal center type. Immunohistochemical stains performed demonstrated that the neoplastic lymphocytes were positive for CD79a and CD10, consistent with a germinal center phenotype of DLBCL (Figure 1). Stains for *BCL2* and *MYC* proteins were both positive and the Ki-67 proliferation index was approximately 95% (Figure 1). Concurrent flow cytometric analysis identified a CD10(+) monoclonal lambda B-cell population. The PET CT scan showed widespread, FDG avid lymphadenopathy within the neck, chest, abdomen, and pelvis, hypermetabolic mural thickening about the splenic flexure of colon, and multiple FDG avid osseous lesions.

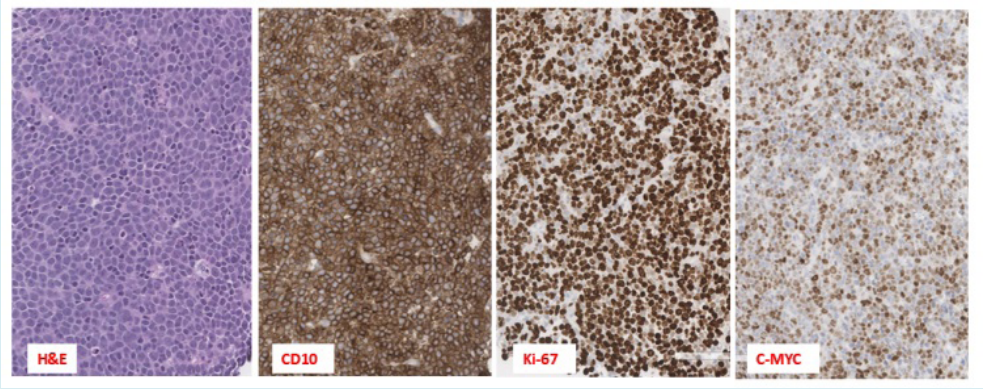

Figure 1: Immunohistochemical Stain of Retroperitoneal Mass Biopsy For CD10, Ki-67 and C-*MYC* Proteins.

A bone marrow evaluation demonstrated a hypercellular bone marrow (50-60%) involved by DLBCL, comprising approximately 40-50% of the bone marrow cellularity. Immunohistochemical staining performed on the core biopsy was positive for CD10, CD20, *BCL2*, *BCL6*, and *MYC*, and negative for CD3, CD5, MUM1, cyclin D1, and EBV. The Ki-67 proliferation index was approximately 70%. A lumbar puncture with flow cytometry was negative for lymphoma involvement, and a dose of intrathecal methotrexate was given after the procedure. An MRI of the brain did not show any evidence of lymphoma in the CNS.

Conventional cytogenetics performed on the bone marrow specimen demonstrated a complex karyotype with multiple numeric and structural abnormalities, including t(3;8) and t(14;18) (Table 1). FISH using DNA probes specific for the *MYC* region at 8q24 and *BCL6* region at 3q27 had an abnormal atypical signal pattern. Metaphase FISH confirmed a t(3;8) rearrangement along with additional rearranged signals of *BCL6* and *MYC* on the homologous chromosome 8 (Figures 2 & 3). A FISH study performed on bone marrow clot specimen showed abnormal atypical signal patterns for *MYC* and *BCL6* break apart probes, 2 signals for 5'*MYC* and 1 signal for 3'*MYC*, 1 fused *BCL6* signal, 3 signals for 5'*BCL6* and 1 signal for 3'*BCL6*, respectively. FISH showed typical signal pattern for t(14;18) IGH::*BCL2* rearrangement. Together, both interphase and metaphase FISH results confirmed a very rare *BCL6*::*MYC* [t(3;8)] rearrangement. This result is consistent with high-grade B-cell lymphoma with *BCL6*::*MYC*, and IGH::*BCL2* gene rearrangements. Molecular studies were not performed.

CASE #	HANS	Age	Sex	IHC	CD10	Ki-67 (%)	CD5	CD20	Conventional Karyotype	PCR	FISH	References
Study case	GC	65	F	*MYC* (+); *BCL2* (+); *BCL6*(+)	+	95	-	-	45-48,XX,add(1)(q42),del(2)(q33q35),t(3;8)(q27;q24.1),+7,+7, t(14;18)(q32;q21.3),-15, add(18)(q23),der(19)t(15;19)(q15;q13.3)[cp9]/46, XX[11]	NP	Interphase FISH: *MYC* nuc ish (5'*MYC*x2, 3'*MYC*x1)[77/200] *BCL6* nuc ish(5'*BCL6*x4,3'*BCL6*x2)(5'*BCL6* con 3'*BCL6*x1)[111/200] *BCL2* nuc ish(IGH,*BCL2*)x3(IGH con *BCL2*x2)[78/100]; Metaphase FISH: ish der(8)t(3;8)(q27;q24.1)(5'*MYC*+,3'*MYC*-,5'*BCL6*-,3'*BCL6*+)x2 ish der(3)ins(3)(p25)(3'*BCL6*+)t(3;8)(5'*BCL6*-,5'*MYC*-,3'*MYC*+)	Study case
1	GC	53	F	*MYC* (NR); *BCL2* (+); *BCL6*(+)	+	40	-	+	48,XX,t(3;8)(q27;q24.1), del(6)(q21q23),+12, +18[7]/46, XX[1]	IGH::*BCL2* fusion transcript negative	t(3;8)(q27;q24.1)	Wang HY, et al. [8]
2	non-GC	66	F	*MYC* (>90% +); *BCL2* (+); *BCL6* (+)	-	NR	-	+	47,XX,dup(1)(q25q32),?del(8)(q24),+13,del(13)(q13q21)x2,add(14)(q3?1)[cp11]/46, XX[15]	NR	Metaphase FISH: ish dup(1)(q25q32)(MEGF6+,ABL2++),t(3;8;14)(q27;q24;q32)(3'*BCL6*+,5'*BCL6*-,5'IgH+;5'*MYC*+, 3'*MYC*-,5'*BCL6*;3'IgH+,5'IgH-,3'*MYC*+),del(13)(q13q21)(D13S319-, LAMP1+)x2	De Paoli E, et al. [9]
3	non-GC	37	F	*MYC* (NR); *BCL2* (-); *BCL6*(NR)	-	100	-	+	46,XX,t(3;8)(q27;q24)[7]/46,XX[3]	NR	Interphase FISH: *BCL6* nuc ish(*BCL6*x2)(5'*BCL6* sep 3'*BCL6*x1)[12/100] *MYC* nuc ish(*MYC*x2)(5'*MYC* sep 3'*MYC*x1)[11/100] *BCL6*::*MYC* nuc ish(*BCL6*,*MYC*)x3(*BCL6* con *MYC*x2)[14/100]; Metaphase FISH: ish t(3;8)(q27;q24)(5'*MYC*+;3'*MYC*+)	Sanders L, et al. [3]
4	GC	72	M	*MYC* (NR); *BCL2* (-); *BCL6*(+)	+	100	-	+	47,XY,inv(2)(p11q21),t(3;8)(q27;q24),del(6)(q23q25),+12,–13, t(14;18)(q32;q21)[9]/46,XY	NP	NR/NP	Motlló C, et al. [10]

5	GC	44	F	*MYC* (NR); *BCL2* (-); *BCL6*(+)	+	95	NR	NR	48,XX,t(3;8) (q27;q24),−4,add(7) (q21.2),+der(8)t(3;8) (q27;q24), add(11) (q22),add(12) (p13),t(14;18) (q32;q21),+mar1, +mar2	IGH:: *BCL2* fusion product.	NR/NP	Motlló C, et al. [10]
6	GC	53	M	*MYC* (NR); *BCL2* (NR); *BCL6*(NR)	NR	NR	NR	NR	48,XY,del(2)(q34),t(3;8) (q27;q24),+7,+der(8) t(3;8),t(14;18) (q32;q21) [18]	NR/NP	NR/NP	Bertrand P, et al. [11]
7	GC	56	F	*MYC* (NR); *BCL2* (NR); *BCL6*(NR)	NR	NR	NR	NR	49,XX,t(3;8) (q27;q24),+7,+der(8) t(3;8),del(10) (q24q25),+12,t(14;18) (q32;q21) [20]	NR/NP	NR/NP	Bertrand P, et al. [11]

NP - Not performed; NR – Not reported.

Table 1: Cases with *BCL6*::*MYC* rearrangement in DLBCL.

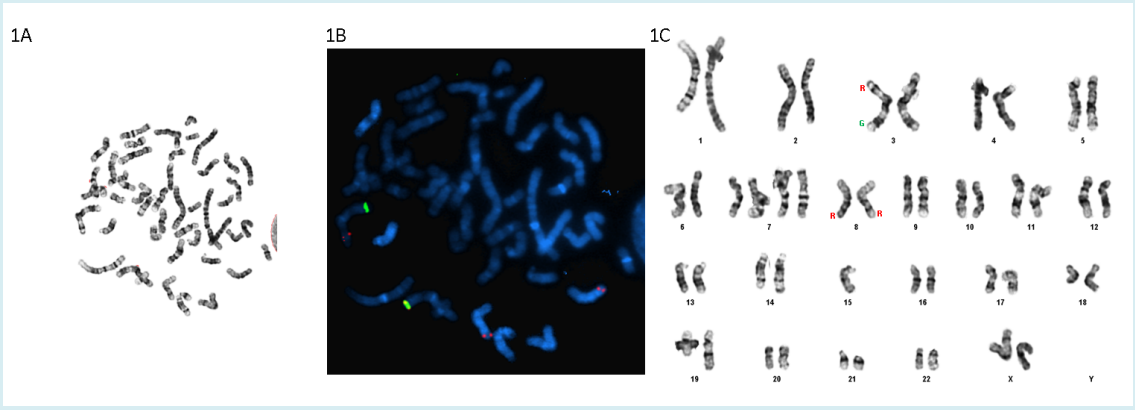

Figure 2: Showing *BCL6* (3q27) Break Apart Probe FISH Signal Translocation to Chromosome 8 Long Arm (Tel 5'*BCL6* Red [R]; Cen 3'*BCL6* Green [G]). A. G-band metaphase; B. Reverse G-band Metaphase; C. Karyogram with Representation of the *BCL6* Rearranged Signals.

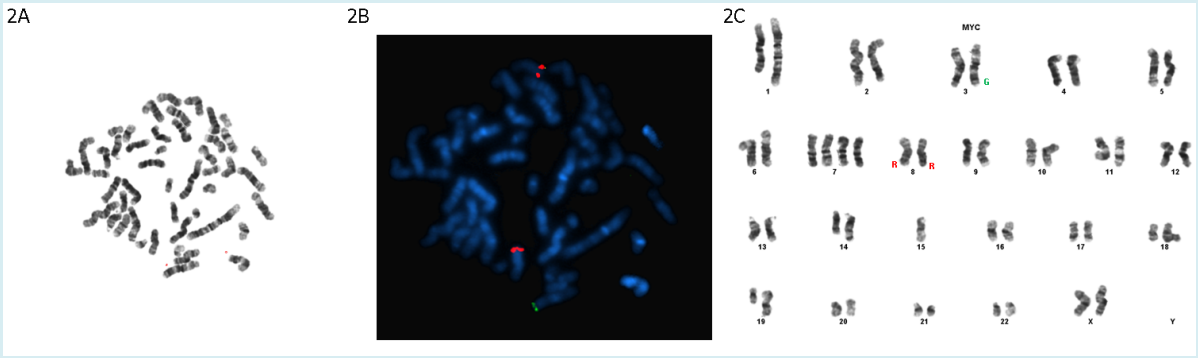

Figure 3: Showing *MYC* (8q24) Break Apart Probe FISH Signal Translocation to Chromosome 3 Long Arm (Cen 5'*MYC* Red [R]; Tel 3'*MYC* Green [G]). A. G-band metaphase; B. Reverse G-band; Metaphase C. Karyogram with Representation of the *MYC* Rearranged Signals.

The patient began treatment with R-CHOP. Soon after beginning treatment the patient had a recurrence of diarrhea and abdominal pain and was re-admitted for *C. difficile* colitis. A CT performed demonstrated that there was significant lymphoma progression, and it was apparent that the lymphoma progressed through R-CHOP chemoimmunotherapy. The patient then started treatment with Tafasitamab and Lenalidomide as a subsequent therapy. She continued to decline and opted for palliative care, succumbing two weeks later.

Discussion

Analysis of *MYC*, *BCL2* and *BCL6* regions is essential in identifying high-risk patients. Lymphomas with *MYC* and *BCL2*, and/or *BCL6* rearrangements are known as high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, previously called DHL or THL and are associated with a poor clinical outcome.

The t(3;8) is a rare rearrangement seen in DLBCL. The oncogenic effect of the t(3;8) rearrangement is heterologous activation of *MYC* by the *BCL6* locus enhancer and therefore is equivalent to a single-hit *MYC*-activating rearrangement [5-7]. The FISH study performed on the bone marrow clot showed abnormal atypical signal patterns for *MYC* and *BCL6* break-apart probes and typical signal pattern for t(14;18) IGH::*BCL2* rearrangement. The identification of *BCL6*::*MYC* fusion using interphase FISH using break-apart probes is indistinguishable from more conventional DHL with independent *MYC* and *BCL6* translocations.

The median overall survival of <2 years has been reported in DHL cases. A worse prognosis has been associated for DHL patients with additional clinicopathologic features including bone marrow involvement and IG::*MYC* rearrangement. Based on the literature review we identified seven cases of DLBCL with the reported *BCL6*::*MYC* gene rearrangement. Six of these cases showed t(3;8) by conventional cytogenetics. Only one had a cryptic three-way translocation involving chromosomes 3, 8, and 14. Our case is the first case which showed rare cryptic translocation involving chromosomes 3 and 8. Based on the data available for survival in some of the patients listed in Table 1, the median age was 59 years. Our patient had a significant mass effect with an abdominal mass over 20 cm, similar to Case #5 (Table 1) who developed a mass and had the worst outcome of the cases listed, with an average survival time of 3.5 months in these two cases. Overall survival data is limited due to few reported cases with this rearrangement.

Identifying more cases with similar rare translocations involved in DHL compared to typical DHL may help to better delineate such a rare entity. This case displays the crucial role of metaphase FISH in identifying specific chromosome partners involved in the translocation which are indistinguishable by the interphase FISH especially using FISH break apart probes. Although DLBCLs with DHL now known as high-grade B-cell lymphomas are associated with an overall survival at 3 years [12], presence of very rare *BCL6*::*MYC* with typical IGH::*BCL2* gene rearrangements in DLBCL lymphomas along with additional comorbidities may have shorter survival rate.

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