

Case Report

Primary diffuse large B-cell lymphoma of the central nervous system harboring a reciprocal t(3;13)(q27;q14): a case report

Masahiro Manabe¹, Ryuta Matsuoka², Dai Momose¹, Yasuyoshi Sugano¹, Eiwa Ishida³, Ki-Ryang Koh¹

Departments of ¹Hematology, ³Pathology, Osaka General Hospital of West Japan Railway Company, 1-2-22 Matsuzaki-cho, Abeno-ku, Osaka 545-0053, Japan; ²Department of Neurosurgery, Osaka General Medical Center, 3-1-56 Bandaihigashi, Sumiyoshi-ku, Osaka 558-8558, Japan

Received March 1, 2016; Accepted May 23, 2016; Epub July 1, 2016; Published July 15, 2016

Abstract: A case of primary diffuse large B-cell lymphoma of the central nervous system involving a t(3;13)(q27;q14) chromosomal abnormality is reported. The disease exhibited an aggressive clinical course. As far as we know, there have only been 8 cases of lymphoma harboring this type of chromosomal translocation, and none of them involved the central nervous system. This is the first reported case of the primary diffuse large B-cell lymphoma of the central nervous system involving a reciprocal t(3;13)(q27;q14) translocation.

Keywords: Primary diffuse large B-cell lymphoma of the central nervous system, t(3;13)(q27;q14), BCL6

Introduction

Translocations involving the B-cell lymphoma 6 (BCL6) gene locus (3q27) are seen in approximately 30-40% of diffuse large B-cell lymphomas of the central nervous system (CNS DLBCL) [1]. A reciprocal translocation containing 3q27 and 13q14 breakpoints, t(3;13)(q27;q14), has been reported in 8 cases of various lymphoid neoplasms as a rare but recurring chromosomal translocation (Table 1) [2-7]. These cases included 3 cases of follicular lymphoma, 3 cases of Burkitt's lymphoma, and 1 case each of nodal marginal zone B-cell lymphoma and systemic DLBCL. However, there have not been any reports about CNS DLBCL involving t(3;13)(q27;q14). Here, we present a case of CNS DLBCL harboring t(3;13)(q27;q14).

Clinical summary

A 66-year-old female developed memory disturbance over the course of a month. No lymphadenopathy was detected, and the patient did not have a history of night sweats or body weight loss. Mass lesions were found in the splenium of the corpus callosum and the right cerebellum on magnetic resonance imaging (Figure 1A, 1B). The patient had a lactate

dehydrogenase level of 337 U/L, and a soluble interleukin-2 receptor level of 313 U/mL. Tests for hepatitis B virus antigen, hepatitis C virus antibody, and human immunodeficiency virus antigen were negative. A serological examination did not obtain any evidence of an acute or recent Epstein-Barr virus infection (viral capsid antigen-IgM: <10, IgG: positive, and Epstein-Barr nuclear antigen: positive). Partial resection of the mass in the splenium was performed via a craniotomy. A biopsy of the mass in the splenium demonstrated the massive proliferation of large lymphoid cells with large, polymorphic, eccentrically located nuclei (in some cells) and prominent nucleoli. Immunohistochemical staining revealed that the large atypical lymphocytes were positive for CD20, BCL2, and multiple myeloma oncogene 1 (MUM1), and partially positive for CD5. On the other hand, the atypical lymphocytes were negative for CD10, CD138, and Epstein-Barr virus latent membrane protein 1 (LMP1) (Figure 1C-F). A pathological diagnosis of CNS DLBCL was made after an examination of the surgical specimen. Cytogenetic analysis of the tumor cells using the G-banding technique revealed the following findings: 46,X,der(X)(Xqter→Xq13::?:Xp11.2→Xqter),der(3)t(1;3)(q12;q11.2),t(3;13)(q27;q14),del(6)(q12),add(14)(q24)[14]/46,

CNS DLBCL harboring t(3;13)(q27;q14)

Table 1. Cytogenetic findings of previously reported cases involving t(3;13)(q27;q14)

Case no.	Age/ Sex	G-banded Karyotype including t(3;13)(q27;q14)	Diagnosis	Reference
1	81/M	46,XY,add(19)(q?)/46,idem,t(3;13)(q27;q14),del(6)(q?)	FL	Temperani et al. (1996)
2	68/F	46,XX,t(3;13)(q27;q14),t(4;18)(q21;q21)/46,idem,del(6)(q16q24)	DLBCL	Laï et al. (1998)
3	32/F	46,XX,t(3;13)(q27;q14),t(14;18)(q32;q21)/46,XX,t(8;6;13)(q21;q11;p11),t(14;18)	FL	Laï et al. (1998)
4	67/F	46,XX,t(3;13)(q27;q14),+5,-6,del(6)(q15q23),+7,t(8;14)(q24;q32),+mar	BL	Laï et al. (1998)
5	44/M	46,XY,t(3;13)(q27;q14),t(8;22)(q24;q11),t(14;18)(q32;q21),+der(18)t(14;18),+mar	BL	Stamatoullas et al. (2000)
6	NR	48,XX,+X,+del(1)(p21p36),del(6)(q13q21),del(13)(q13q14),t(14;18)(q32;q21)/46,XX,der(1)t(1;1)(p36;q21),t(3;13)(q27;q14),del(6)(q13q21),t(14;18)	FL	Sanchez-Izquierdo et al. (2001)
7	NR	46,XY,der(1)t(1;12)(q42;q13),t(3;13)(q27;q14),del(17)(p11),+der(17)dup(17)(q21q25)t(12;17)(?;q25)t(1;12)(q21;?)	NMZL	Itoyama et al. (2002)
8	82/F	47,XX,t(3;13)(q27;q14),del(8)(q22),der(9)t(9;22)(p13;q11),+12,T(14;18)(q32;q21),der(22)t(9;22)(p13;q11)ins(22;8)(q11;q24q22)	BL	Bacher et al. (2011)
9	66/F	46,X,der(X)(Xqter→Xq13::?:Xp11.2→Xqter),der(3)t(1;3)(q12;q11.2),T(3;13)(q27;q14),del(6)(q12),add(14)(q24)/46,idem,i(15)(q10)	CNS DLBCL	Present case

NR, not reported; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt's lymphoma; NMZL, nodal marginal zone B-cell lymphoma; CNS DLBCL, primary diffuse large B-cell lymphoma of the central nervous system. Except for that seen in the present case, the karyotypes were described according to the system used in the Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer [16].

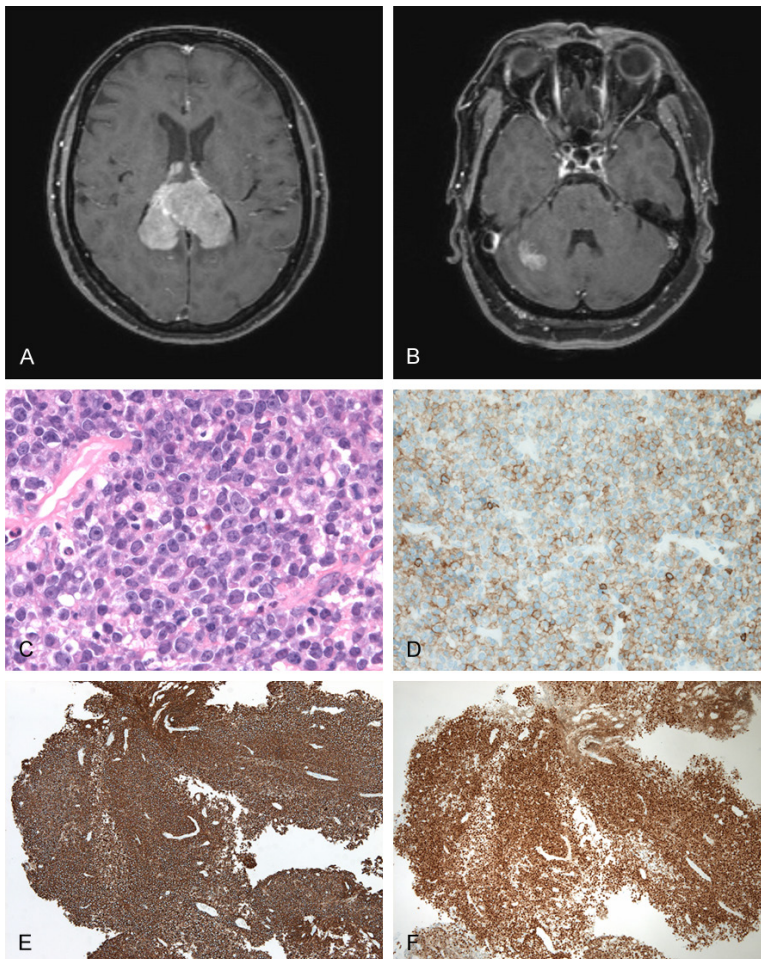


Figure 1. Gadolinium-enhanced T1-weighted magnetic resonance images showing mass lesions in the splenium of the corpus callosum (A) and the right cerebellum (B). Pathological images of the surgical specimen showing infiltration by lymphoid cells. H&E stain (C) and immunohistochemical staining of CD5 (D), CD20 (E), and MUM-1 (F).

idem,i(15)(q10) [6] (**Figure 2A**). The formalin-fixed paraffin-embedded surgical specimen was also subjected to interphase fluorescent *in situ* hybridization (FISH) analysis. *BCL6*, *IGH* break-apart probes demonstrated signal constellations that reflected breaks at the *BCL6*(3q27) and *IGH*(14q32) loci in 69% and 61% of the tumor cells, respectively (**Figure 2B, 2C**). On the other hand, no rearrangement was seen using the *MYC*(8q24) probe.

The patient received chemotherapy involving 375 mg/m² rituximab on day 1, 3.5 g/m² methotrexate on day 2, 1.4 mg/m² vincristine on day 2, and 100 mg/m² procarbazine on days 2 to 8, disease progression was subsequently observed. Due to her poor performance status, the patient was given supportive care alone, and she eventually died 2 months after the initial diagnosis.

Discussion

The *BCL6* gene at 3q27 encodes a zinc-finger tran-

CNS DLBCL harboring t(3;13)(q27;q14)

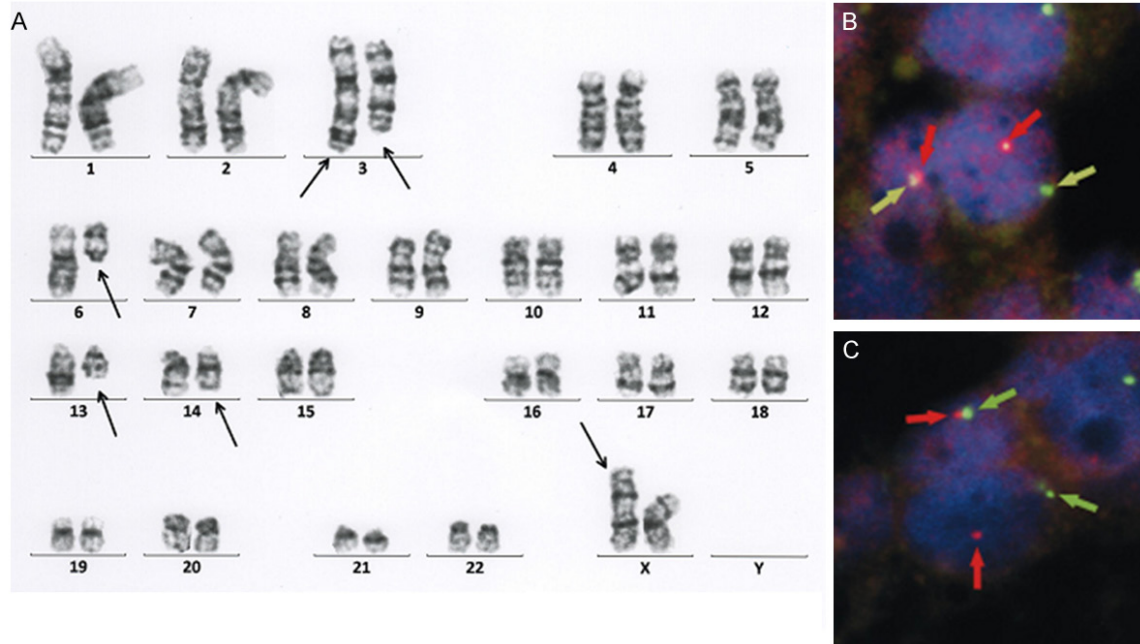


Figure 2. G-banded karyogram obtained in this case. The arrows show derivative chromosomes (A). Results of interphase FISH analysis (B, C). The results of the FISH analysis performed with a *BCL6* break-apart probe (Vysis LSI *BCL6* Dual Color Break Apart Rearrangement Probe, 1N23-30, Abbott Molecular Inc., IL, USA) are shown in (B). One green (3' *BCL6*, green arrows)/red (5' *BCL6*, red arrows) colocalized signal from the unarranged locus and two separate green/red signals can be seen. The results of the FISH analysis performed with an *IGH* break-apart probe (Vysis LSI *IGH* Dual Color Break Apart Rearrangement Probe, 5J73-01, Abbott Molecular Inc., IL, USA) are shown in (C). One red (3' *IGH*, red arrows)/green (5' *IGH*, green arrows) colocalized signal from the unarranged locus and two separate red/green signals can be seen.

scription factor that is expressed in germinal center B cells and functions as a transcriptional repressor [8]. Translocations involving *BCL6* are observed in approximately 30-40% of CNS DLBCL [1]. They can include a variety of non-immunoglobulin partner genes as well as the immunoglobulin heavy locus and kappa and lambda loci, and cause deregulated *BCL6* expression [8]. In a multicenter study, Lai et al. detected three t(3;13)(q27;q14)-harboring lymphoma cases (1.5%) among 210 lymphoid tissues; however, since Temperani et al. [2] first described the case of a patient with follicular lymphoma harboring t(3;13)(q27;q14) in 1996, only 8 cases of lymphoid malignancies with this translocation have been reported. Hence, it seems that the original estimate of the incidence of this translocation (1.5%) might be too high. Furthermore, except for our case there have not been any reports about cases of CNS DLBCL harboring this translocation; therefore, it seems that the present case is the first reported case of CNS DLBCL to involve the t(3;13)(q27;q14) translocation.

In a detailed analysis of two B-cell lymphoma patients with t(3;13)(q27;q14), Galiègue-Zouitina et al. [9] reported that the translocation resulted from the juxtaposition of the *BCL6* sequence on chromosome 3q27 with the L-plastin (*LCP1*) sequence on chromosome 13q14. Although *BCL6* rearrangement was confirmed by FISH in the present case, we could not perform any detailed genetic analysis of the partner gene of *BCL6*; i.e., *LCP1*, because of the lack of a tissue specimen. Further accumulation of cases will be required to enable the lymphomagenesis mechanism responsible for t(3;13)(q27;q14)-containing lymphoid malignancies to be elucidated via molecular and genetic analyses.

As for the prognostic significance of t(3;13)(q27;q14), it was reported that *BCL6* rearrangement is correlated with better outcomes in DLBCL [10], although another study obtained a different result [11]. However, it was suggested that previous cases involving the t(3;13)(q27;q14) translocation tended to also exhibit

another chromosomal abnormality, del (6q), and most of them demonstrated a poor prognosis [3]. In a study of CNS DLBCL based on comparative genomic hybridization technique, Rickett et al. demonstrated that CNS DLBCL displays a mean of 5.5 chromosomal changes per tumor [12]. Among these changes, the loss of 6q was most common (50%), and other studies obtained similar findings (frequency of 6q loss: 45-47%) [13, 14]. Concerning its prognostic impact, several studies have found that the loss of 6q is significantly correlated with shorter survival [12, 14, 15]. In addition, abnormalities of chromosome arm 1q have been suggested to be correlated with a poor prognosis [6]. In the current case, chromosomal analysis detected both del (6q) and an abnormality of the 1q arm; hence, we selected a high-dose methotrexate-containing regimen for the induction chemotherapy, but tumor progression was subsequently observed. Although it has been established that high-dose methotrexate regimens represent the optimal therapy for CNS DLBCL, we suggest that high-risk cases of CNS DLBCL involving poor prognostic factors, such as del (6q) and 1q abnormalities, as were seen in the present study, might require more powerful treatments, for example, a combination of high-dose methotrexate and cytosine arabinoside.

Disclosure of conflict of Interest

None.

Address correspondence to: Masahiro Manabe, Department of Hematology, Osaka General Hospital of West Japan Railway Company, 1-2-22 Matsuzaki-cho, Abeno-ku, Osaka 545-0053, Japan. Tel: 81-6-6628-2221; Fax: 81-6-6628-4707; E-mail: m115-3564@med.osaka-cu.ac.jp

References

- [1] Kluin PM, Deckert M, Ferry JA. Primary diffuse large B-cell lymphoma of the CNS. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Edited by Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. Lyon: IARC Press; 2008. pp. 240-241.
- [2] Temperani P, Gandini G, Volinia S, Giacobbi F, Vaccari P, Waterfield MD, Emilia G. YAC clone H10 discriminates between 3q26.2 and 3q27 chromosome rearrangement in hematological disorders. *Leukemia* 1996; 10: 225-228.
- [3] Lai JL, Daudignon A, Kerckaert JP, Galiègue-Zouitina S, Detourmignies L, Morel P, Bauters F, Fenaux P. Translocation (3;13)(q27;q14): a nonrandom and probably secondary structural change in non-Hodgkin lymphomas. *Cancer Genet Cytogenet* 1998; 103: 140-143.
- [4] Stamatoullas A, Buchonnet G, Lepretre S, Lenain P, Lenormand B, Duval C, Callat MP, Gaulard P, Bastard C, Tilly H. *De novo* acute B cell leukemia/lymphoma with t(14;18). *Leukemia* 2000; 14: 1960-1966.
- [5] Sanchez-Izquierdo D, Siebert R, Harder L, Marugan I, Gozzetti A, Price HP, Gesk S, Hernandez-Rivas JM, Benet I, Solé F, Sonoki T, Le Beau MM, Schlegelberger B, Dyer MJS, Garcia-Conde J, Martinez-Climent JA. Detection of translocations affecting the *BCL6* locus in B cell non-Hodgkin's lymphoma by interphase fluorescence *in situ* hybridization. *Leukemia* 2001; 15: 1475-1484.
- [6] Itoyama T, Nanjungud G, Chen W, Dyomin VG, Teruya-Feldstein J, Jhanwar SC, Zelenetz AD, Chaganti RSK. Molecular cytogenetic analysis of genomic instability at the 1q12-22 chromosomal site in B-cell non-Hodgkin lymphoma. *Genes Chromosomes Cancer* 2002; 35: 318-328.
- [7] Bacher U, Haferlach T, Alpermann T, Kern W, Schnittger S, Haferlach C. Several lymphoma-specific genetic events in parallel can be found in mature B-cell neoplasms. *Genes Chromosomes Cancer* 2011; 50: 43-50.
- [8] Basso K and Dalla-Favera R. *BCL6*: master regulator of the germinal center reaction and key oncogene in B cell lymphomagenesis. *Adv Immunol* 2010; 105: 193-210.
- [9] Galiègue-Zouitina S, Quief S, Hildebrand MP, Denis C, Detourmignies L, Lai JL, Kerckaert JP. Nonrandom fusion of *L-plastin (LCP1)* and *LAZ3 (BCL6)* genes by t(3;13)(q27;q14) chromosome translocation in two cases of B-cell non-Hodgkin lymphoma. *Genes Chromosomes Cancer* 1999; 26: 97-105.
- [10] Offit K, Lo Coco F, Louie DC, Parsa NZ, Leung D, Portlock C, Ye BH, Lista F, Filippa DA, Rosenbaum A, Ladanyi M, Jhanwar S, Dalla-Favera R, Chaganti RSK. Rearrangement of the *bcl-6* gene as a prognostic marker in diffuse large-cell lymphoma. *N Engl J Med* 1994; 331: 74-80.
- [11] Muramatsu M, Akasaka T, Kadowaki N, Ohno H, Yamabe H, Edamura S, Doi S, Mori T, Okuma M, Fukuhara S. Rearrangement of the *BCL6* gene in B-cell lymphoid neoplasms: comparison with lymphomas associated with *BCL2* rearrangement. *Br J Haematol* 1996; 93: 911-920.
- [12] Rickert CH, Dockhorn-Dworniczak B, Simon R, Paulus W. Chromosomal imbalances in prima-

CNS DLBCL harboring t(3;13)(q27;q14)

- ry lymphomas of the central nervous system. *Am J Pathol* 1999; 155: 1445-1451.
- [13] Weber T, Weber RG, Kaulich K, Actor B, Meyer-Puttlitz B, Lampel S, Büschges R, Weigel R, Deckert-Schlüter M, Schmiedek P, Reifenberger G, Lichter P. Characteristic chromosomal imbalances in primary central nervous system lymphomas of the diffuse large B-cell type. *Brain Pathol* 2000; 10: 73-84.
- [14] Cady FM, O'Neill BP, Law ME, Decker PA, Kurtz DM, Giannini C, Porter AB, Kurtin PJ, Johnston PB, Dogan A, Remstein ED. Del(6)(q22) and *BCL6* rearrangements in primary CNS lymphoma are indicators of an aggressive clinical course. *J Clin Oncol* 2008; 26: 4814-4819.
- [15] Nakamura M, Kishi M, Sakaki T, Hashimoto H, Nakase H, Shimada K, Ishida E, Konishi N. Novel tumor suppressor loci on 6q22-23 in primary central nervous system lymphomas. *Cancer Res* 2003; 63: 737-741.
- [16] Mitelman F, Johansson B and Mertens F (Eds). *Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer (2016)*. <http://cgap.nci.nih.gov/Chromosomes/Mitelman>. Accessed 1 Feb 2016.