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【 CASE REPORT 】

Biclonal Diffuse Large B-cell Lymphoma Commonly Characterized by Partial Trisomy 18q Involving *MALT1* and *BCL2*

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Abstract:
A 68-year-old man was admitted because of a left shoulder mass and swollen right testis. Pathological examinations indicated a diagnosis of diffuse large B-cell lymphoma (DLBCL) with the CD20+BCL6+MUM1+ BCL2+CD10-MYC- phenotype in both lesions. G-banding of soft tissue showed 47,XY,+18, whereas testicular cells showed 47,X,+X,-Y,der(4)t(4;18)(p15;?),del(5)(q?),+13. Fluorescence *in situ* hybridization detected additional *MALT1* and *BCL2* signals in both lesions. Southern blot demonstrated different *IGH* rearrangements between the soft tissue and testis. The patient was diagnosed with biclonal DLBCL with different karyotypes but similar immunophenotypes. Partial trisomy 18q involving *MALT1* and *BCL2* may be commonly involved in the pathogenesis of this biclonal DLBCL.

Key words: diffuse large B-cell lymphoma, biclonal B-cell lymphoma, trisomy 18, *MALT1*, *BCL2*

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive neoplasm of large B lymphoid cells and is the most common subtype of adult non-Hodgkin's lymphoma. Cytogenetically, 3q27 translocations involving *BCL6*, t(14;18)(q32;q21.3) involving *BCL2*, and *MYC* rearrangements at 8q24 are detected in about 30%, 20-30%, and 8-14% of DLBCL cases, respectively (1). In addition, various numerical changes, such as gains of chromosomes 3, 7, 12, and X, are frequently found. Among these, trisomy 18 is observed with other chromosome abnormalities in 10-20% of DLBCL cases (2, 3). That is, trisomy 18 is often accompanied by trisomies 3, 7, 12, and 21, loss of 6q, and t(14;18)(q32;q21) or other 14q32 translocations, whereas trisomy 18 as a sole abnormality has not been reported in DLBCL (4, 5).

B-cell chronic lymphoproliferative disorders (B-CLPD), including B-cell lymphomas, are generally considered to result from monoclonal expansions of a single B-cell clone with identical rearrangements of the immunoglobulin heavy chain (*IGH*) gene. However, the appearance of more than one clone has been occasionally observed in B-CLPD (6, 7). In addition to the coexistence of two histologically distinct composite lymphomas (7, 8), one disease with two distinct clones - biclonal B-cell lymphoma - has also been rarely reported (9-12).

We herein report an unusual case of DLBCL that harbored trisomy 18 as the sole cytogenetic abnormality in the soft tissue mass. The testicular mass showed a different and complex karyotype with a different *IGH* rearrangement. Further cytogenetic analyses revealed partial trisomy 18q involving *MALT1* and *BCL2* in both lesions, suggesting a common pathogenic role for this alteration.

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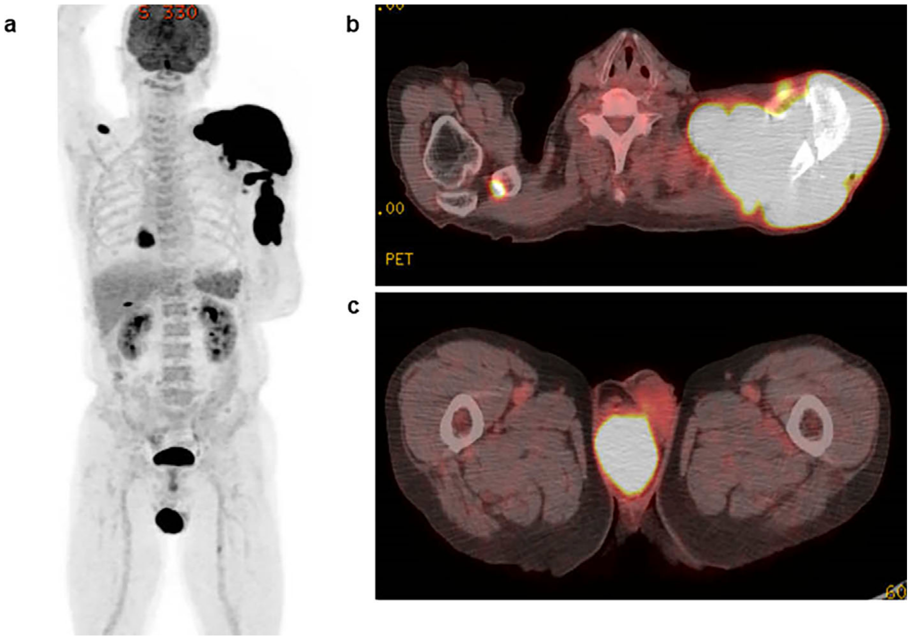

Figure 1. Radiological findings at the diagnosis. (a) ^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) of the whole body shows an increased glucose uptake in the left shoulder, involving the humerus, scapula, and surrounding soft tissue. Furthermore, the uptake of glucose is evident in the right testis and right mediastinal and axillar lymph nodes. The maximum standardized uptake value is 22.3. (b, c) Integrated FDG-PET/computed tomography shows an increased glucose uptake in the left shoulder (b) and right testis (c).

Case Report

A 68-year-old man was admitted to our hospital because of a left shoulder mass and pain. Peripheral blood showed hemoglobin 11.3 g/dL, platelets 230×10^9/L, and leukocytes 10.1×10^9/L with 72% segmented neutrophils, 20% monocytes, 7% lymphocytes, and 1% atypical lymphocytes. Serum levels of lactate dehydrogenase and soluble interleukin-2 receptor were elevated to 534 U/L (normal range, 124-222) and 8,426 U/mL (121-613), respectively. Integrated positron emission tomography/computed tomography showed an increased glucose uptake in the left shoulder involving the humerus, scapula, and surrounding soft tissue (Fig. 1). Furthermore, the uptake of glucose was evident in the swollen right testis.

A pathological analysis of soft tissue in the left shoulder mass showed diffuse proliferation of atypical large lymphoid cells (Fig. 2a). These cells were positive for CD20, BCL6, MUM1, and BCL2 but negative for CD10 and MYC. The Ki-67-positive rate was about 80% (Fig. 2b-h). Immunophenotyping with flow cytometry (FCM) showed that gated cells were positive (>20%) for CD19, CD20, CD22, CD25, CD79a, CD11c and κ-chain but negative for CD10 and CD 38 (Fig. 3a). These findings indicated a diagnosis of DLBCL, NOS, non-germinal center B-cell (non-GCB) subtype.

We performed orchidectomy for the right testicular mass. A pathological examination showed marked proliferation of atypical large lymphoid cells that were destroying seminiferous tubules (Fig. 2i). These cells were positive for CD20, BCL6, MUM1, and BCL2 but negative for CD10 and MYC. About 80% of cells were positive for Ki-67 (Fig. 2j-p). FCM showed that gated cells were positive for CD19, CD 20, CD22, CD25, CD79a, CD38 and κ-chain but negative for CD10 and CD11c (Fig. 3b). These findings confirmed a diagnosis of DLBCL, NOS, non-GCB subtype.

A chromosome analysis of soft tissue cells showed 47, XY,+18[20] (Fig. 4a), whereas testicular cells showed a different and complex karyotype: 47,X,+X,-Y,add(4)(p11),add(5)(q11.2),+13[12] (Fig. 5a). Southern blot analyses of the soft tissue and testicular cells demonstrated rearrangements of *IGH*, but the size of the rearranged bands differed between the two tissue sites. These differences were detected in EcoRI-, BamHI+HindIII-, and HindIII-digested DNAs, indicating the presence of distinct clones (Fig. 6).

For the further characterization of the complex karyotype, we performed spectral karyotyping (SKY) for testicular cells and found that part of chromosome 18 had attached to chromosome 4, resulting in partial trisomy 18 (Fig. 5b). Therefore, the karyotype was revised to 47,X,+X,-Y,der(4)t(4;18)(p15;?),del(5)(q?),+13. To examine the involvement of *MALT1* at 18q21.32 and *BCL2* at 18q21.33 in the fragment of chromosome 18, we performed fluorescence *in situ* hybridization (FISH) with these probes on metaphase spreads. As expected, additional *MALT1* and *BCL2* signals were detected on the der(4)t(4;18) (Fig. 5c, d). FISH on interphase nuclei also confirmed three signals of *MALT1* and *BCL2*.

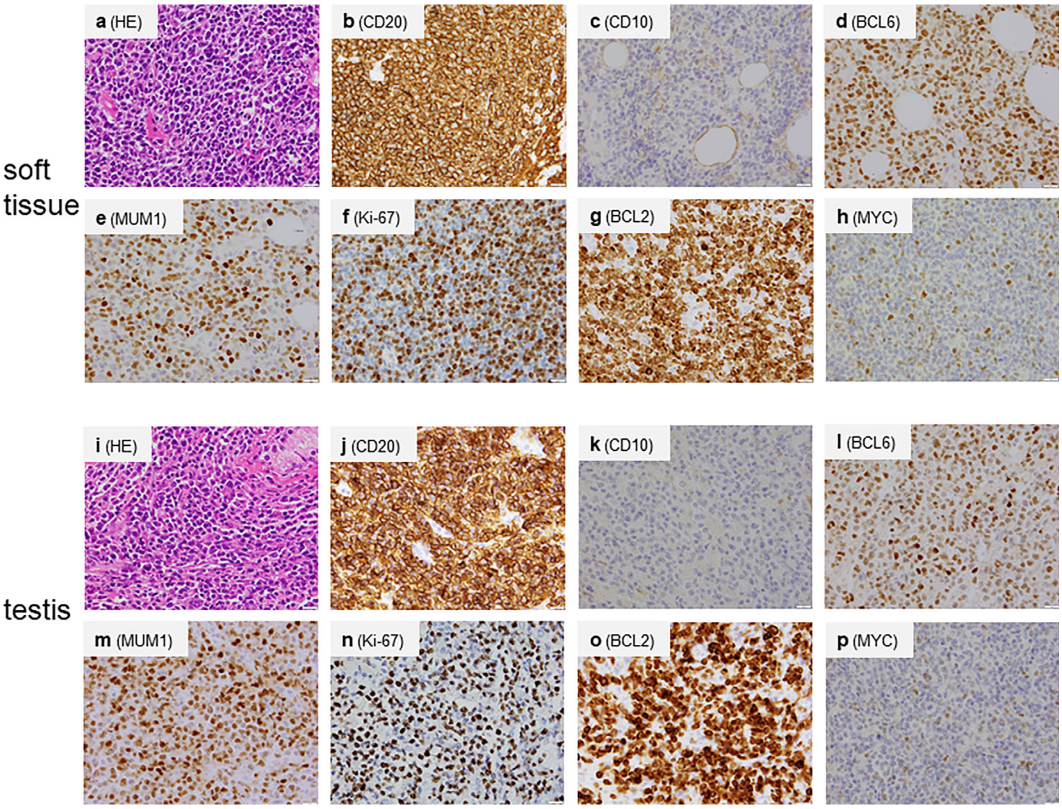

Figure 2. Pathological findings of the soft tissue and testis. (a) Hematoxylin and Eosin (H&E) staining soft tissue shows diffuse proliferation of large-sized atypical lymphoid cells with irregular nuclei (×400). (b)-(h) Immunohistochemistry of soft tissue. Almost all lymphoma cells are diffusely and strongly positive for CD20 (b), BCL6 (d), MUM1 (e) and BCL2 (g). Only 10% of lymphoma cells are positive for CD10 (c) and MYC (h). The Ki-67-positive rate is about 80% (f). (i) H&E staining testis shows marked proliferation of large-sized atypical lymphoid cells destroying seminiferous tubules (×400). (j)-(p) Immunohistochemistry of testis. Almost all lymphoma cells are diffusely and strongly positive for CD20 (j), BCL6 (l), MUM1 (m) and BCL2 (o), but negative for CD10 (k) and MYC (p). The Ki-67-positive rate is about 80% (n).

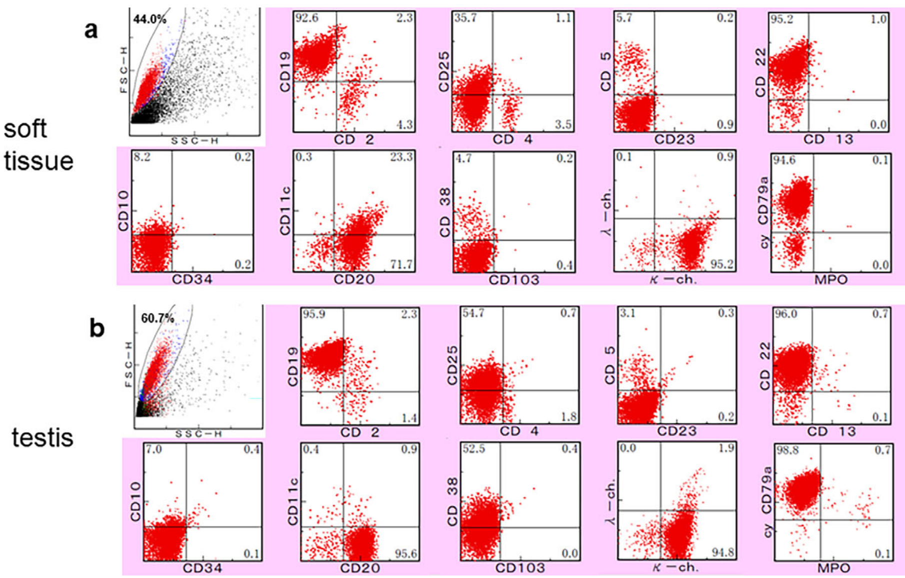

Figure 3. Results of a flow cytometric analysis of lymphoma cells in the soft tissue (a) and testis (b) by forward scatter (FSC)/side scatter (SSC) gating. The corresponding cell percentages demarcated by the gate are (a) 44.0% and (b) 60.7%. The results of two-color analyses of the indicated markers are shown. The corresponding cell percentages in each fraction are indicated. All of the gated cells are commonly positive (>20%) for CD19, CD20, CD22, CD25, CD79a and κ-chain.

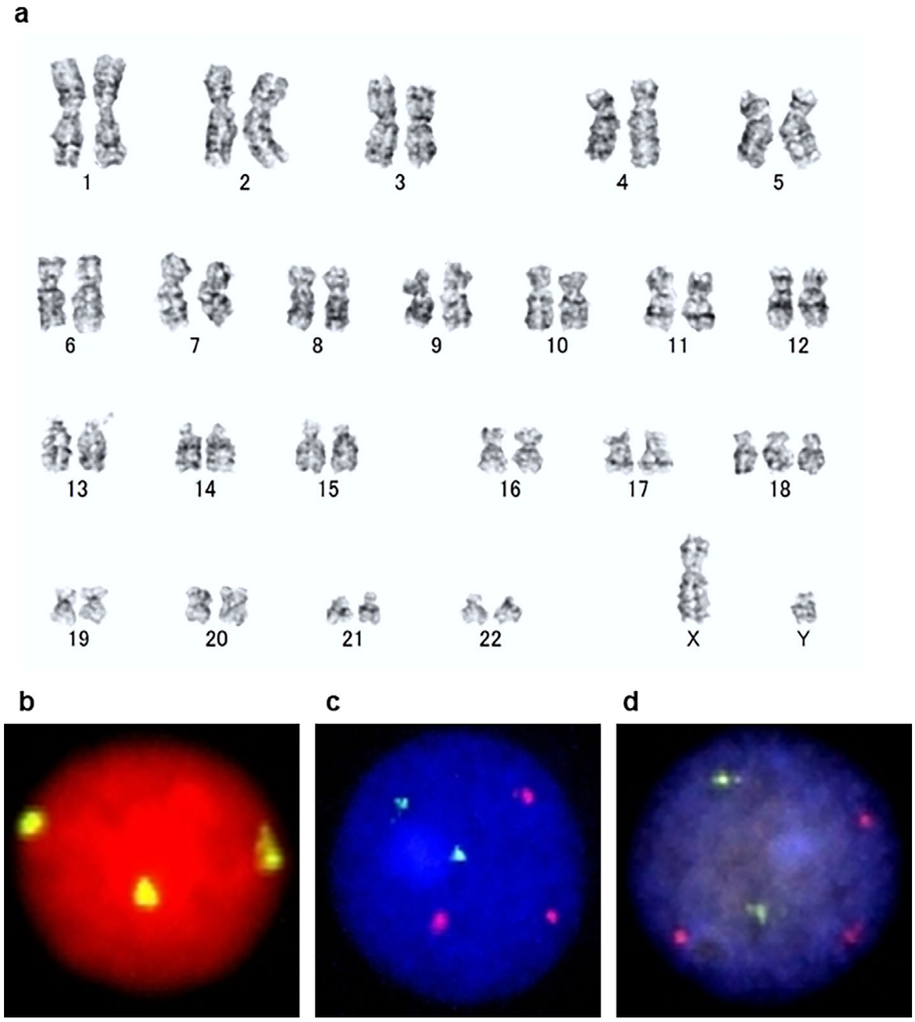

Figure 4. Results of a cytogenetic analysis of the soft tissue. (a) G-banded karyotype of soft tissue cells at diagnosis of DLBCL: 47,XY,+18. (b) Fluorescence *in situ* hybridization (FISH) with a Vysis CEP 18 FISH Probe Kit (Abbott Molecular, Abbott Park, USA) and interphase nuclei. Three CEP18 signals are observed. (c) Interphase FISH with the Vysis LSI IGH/MALT1 Dual Fusion Probe Kit (Abbott Molecular) showing three *MALT1* (red) and two *IGH* (green) signals. (d) FISH with the Vysis LSI IGH/BCL2 Dual Fusion Probe Kit (Abbott Molecular) on interphase nuclei showing three *BCL2* (red) and two *IGH* (green) signals.

We next performed FISH on interphase nuclei of soft tissue cells to confirm trisomy 18. As predicted, FISH detected three signals of CEP 18, *MALT1*, and *BCL2* in interphase cells (Fig. 4b-d).

The patient was diagnosed with DLBCL, clinical stage IV$_A$. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) therapy was started. The response to chemotherapy was rapid, and the left shoulder mass decreased in size. Six courses of R-CHOP therapy induced complete remission (CR). At the time of writing, 18 months after the diagnosis, he remains in CR.

Discussion

We detected trisomy 18 as the sole abnormality in lymphoma cells of the soft tissue and a different complex karyotype in those of the testis in a patient with DLBCL. The size of the *IGH* rearrangement bands differed between the two sites. These distinct cytogenetic and molecular profiles suggested that lymphoma cells of the soft tissue and testis were derived from distinct B-cell clones, although the pathological, immunohistochemical, and immunophenotypic characteristics of both lesions were similar. More specifically, we considered that the DLBCL in the present case was actually a biclonal B-cell lymphoma. Furthermore, SKY and metaphase FISH revealed that *MALT1* and *BCL2* signals were detected on the translocated 18q fragment of der(4)t(4;18)(p15;?), resulting in partial trisomy 18q. Gains of both signals were confirmed on trisomy 18. These results indicate that, despite the biclonal nature of this particular malignancy, partial trisomy 18q involving *MALT1* and *BCL2* may be a common pathogenic driver of DLBCL in the soft tissue and testis.

Trisomy 18 is observed mainly with other chromosome

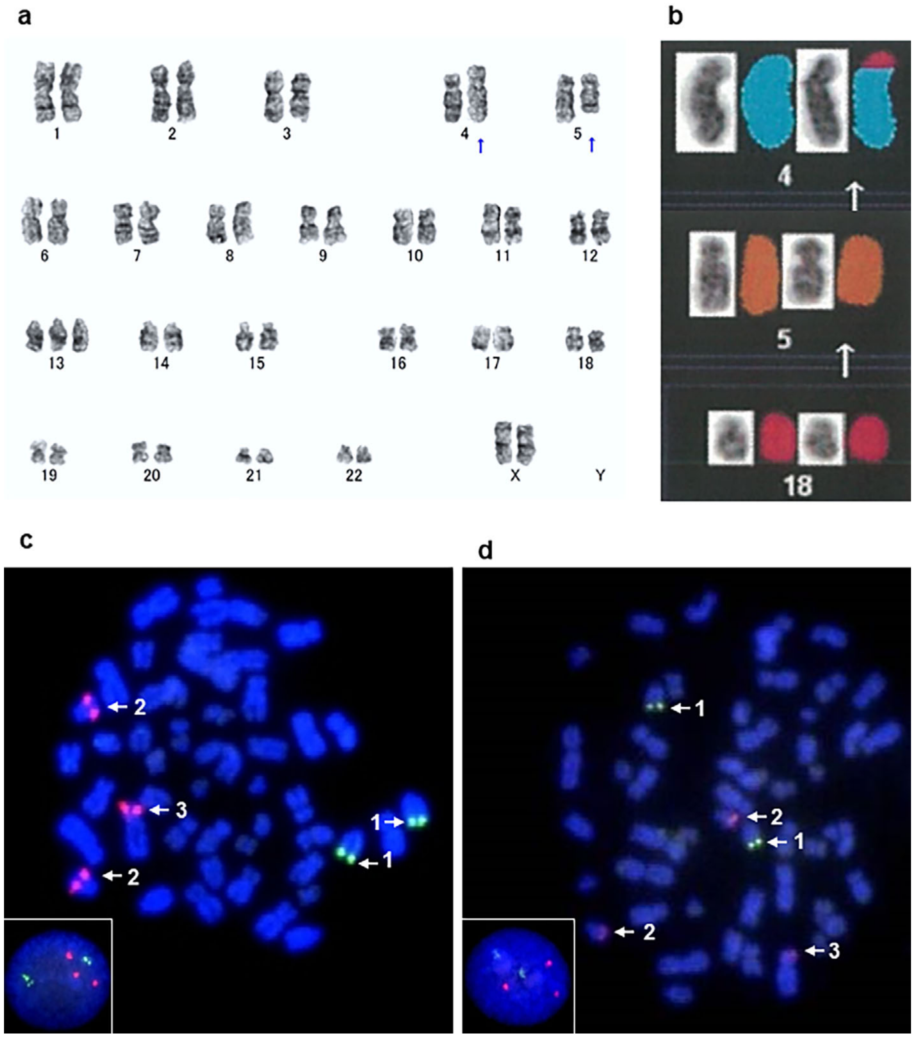

Figure 5. Results of a cytogenetic analysis of the testis. (a) G-banded karyotype of testicular cells at diagnosis of DLBCL: 47,X,+X,-Y,add(4)(p11),add(5)(q11.2),+13. Arrows indicate rearranged chromosomes. (b) Spectral karyotyping (SKY) of metaphase spreads after spectrum-based classification (left side, reverse DAPI; right side, SKY). Only chromosomes 4, 5, and 18 are shown. SKY revealed that the small segment of chromosome 18 had attached to the derivative chromosome 4. The karyotype is revised as 47,X,+X,-Y,der(4)t(4;18)(p15;?),del(5)(q?),+13. Arrows indicate rearranged chromosomes. (c) FISH with Vysis LSI IGH/MALT1 Dual Fusion Probe Kit on metaphase spreads and interphase nuclei. Arrows indicate 1) *IGH* (green) signals on pairs of normal chromosome 14, 2) *MALT1* (red) signals on pairs of normal chromosome 18, and 3) a *MALT1* (red) signal on der(4)t(4;18). Two *IGH* (green) and three *MALT1* (red) signals are also observed on an interphase nucleus (inset). (d) FISH with Vysis LSI IGH/BCL2 Dual Fusion Probe Kit on metaphase spreads and interphase nuclei. Arrows indicate 1) *IGH* (green) signals on pairs of normal chromosome 14, 2) *BCL2* (red) signals on pairs of normal chromosome 18, and 3) a *BCL2* (red) signal on der(4)t(4;18). Two *IGH* (green) and three *BCL2* (red) signals are also observed on an interphase nucleus (inset).

abnormalities in 15-33% of lymphomas, including DLBCL, marginal zone B-cell lymphoma (MZBCL), and follicular lymphoma (FL), but is infrequently found as the primary cytogenetic change (4). According to the Mitelman Database, trisomy 18 as the sole abnormality has been reported in a total of 10 cases of mature B-cell neoplasms: 2 cases of Burkitt lymphoma, 3 cases of FL, and 5 cases of MZBCL (Table) (5, 13-21). Thus, to our knowledge, this is the first case of DLBCL with isolated trisomy 18. Both *MALT1* and *BCL2* are located at 18q21 and have an essential role in MZBCL with t(11;18)(q21;q21) and FL with t(14;18)(q32;q21), respectively. It is assumed that *MALT1* and *BCL2* also play some role in B-cell lymphomas with trisomy 18, although this has not been formally demonstrated. Our results suggest that both *MALT1* and *BCL2* may be associated with the development of B-cell lymphomas with isolated trisomy 18 due to gene dosage effects.

Trisomy 18 has been characterized mainly by MZBCL (21-26). Takimoto et al. detected triple signals of CEP 18, *MALT1* and *BCL2* in MZBCL cells by interphase

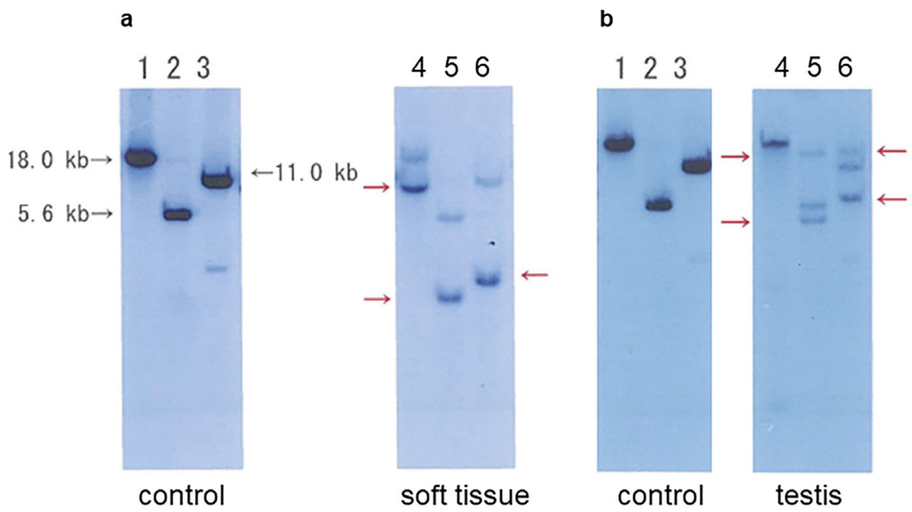

Figure 6. Results of Southern blot analyses of the *IGH* gene using a JH probe. DNA was extracted from the soft tissue (a) and testis (b), digested with EcoRI (lanes 1, 4), BamHI+HindIII (2, 5), or HindIII (3, 6), and subjected to hybridization with a JH probe (SRL, Tokyo, Japan). (a) Lanes 1-3, normal control; lanes 4-6, soft tissue. (b) lanes 1-3, normal control; lanes 4-6, testis tissue. Black arrows indicate germline bands. Red arrows indicate rearranged bands.

Table. Reported Cases of B-cell Lymphomas with Trisomy 18 as a Sole Abnormality.

Case No.	*Age/ Sex*	*Site*	*Dx*	*Karyotypes*	*FISH*	*References*
1	19/F	BM	BL	47,XX,+18/46,XX	ND	(13)
2	32/M	BM	BL	47,XY,+18/46,XY	ND	(13)
3	42/M	NA	FL	47,XY,+18	ND	(14)
4	66/F	Inguinal LN	FL	47,XX,+18[10]/47,idem,del(15)(q15q26)[4]/46,XX[6]	ND	(15)
5	NA/F	NA	FL	47,XX,+18[7]/46,XX,dup(12)(q12q21)[3]	+CEN18 (D18Z1) 61%	(16)
6	55/F	Cervical LN	Nodal MZBCL	47,XX,+18[9]	ND	(17)
7	81/M	PB	Splenic MZBCL	47,XY,+18[2]	ND	(18)
8	NA/F	Spleen	Splenic MZBCL	47,XX,+18/47,idem,del(13)(q12q14)/46,XX	+MALT1, +BCL2, +CEN18	(19)
9	77/F	Lacrimal gland	Extranodal MZBCL	47,XX,+18[3]/46,XX[3]	ND	(20)
10	26/F	Thymus	Extranodal MZBCL	47,XX,+18	+MALT1	(21)
11	68/M	Soft tissue	DLBCL	47,XY,+18[20]	+MALT1, +BCL2, +CEP18 (D18Z1)	Present case

These cases were identified in the Mitelman database using the search terms "mature B-cell neoplasms (all subtypes)" and a sole "+18". Seventeen cases of chronic lymphoid leukemia (CLL) were excluded. Dx: diagnosis, FISH: fluorescence *in situ* hybridization, F: female, M: male, NA: not available, BM: bone marrow, LN: lymph node, PB: peripheral blood, BL: Burkitt lymphoma, FL: follicular lymphoma, MZBCL: marginal zone B-cell lymphoma, DLBCL: diffuse large B-cell lymphoma, ND: not done

FISH, indicating the existence of trisomy 18 (23). They suggested a possible association between trisomy 18 and a large tumor at the initial presentation. Nakamura et al. reported that the presence of extra copies of *MALT1* was significantly associated with the progression or relapse of gastric MZBCL (26). Thus, trisomy 18 can lead to the overexpression of *MALT1* and contribute to the activation of NF-κB, which may play a crucial role in the pathogenesis of MZBCL (21, 25). With regard to DLBCL, Sugimoto et al. detected three *BCL2* and *MALT1* signals using interphase FISH in a case of DLBCL of the uterus (27). In this case, the mass in the greater omentum was diagnosed as MZBCL. Trisomy 18 was detected in both the uterus and greater omentum, suggesting that transformation from MZBCL to DLBCL had occurred. However, the present case had no history of prior low-grade lymphoma. There were no pathological findings of MZBCL or FL in either the soft tissue or testicular lesions. Thus, it is probable that the present case was *de novo* DLBCL rather than transformed DLBCL.

Dierlamm et al. reported that a gain of 18q21 including *MALT1* was detected in 44 of 116 (38%) DLBCL cases and was accompanied by a gain of *BCL2* in 43 cases (28). A gain of 18q21 including *MALT1* was significantly associated with the activated B-cell-like gene expression subtype, increased *BCL2* gene and protein expression, and the differential expression of genes on 18q. Further supporting a cooperative relationship between *MALT1* and *BCL2* is the finding that *MALT1* activates NF-κB, which in turn transcriptionally upregulates *BCL2* (28). Our results underscore the significance of *MALT1* and *BCL2* gains due to trisomy 18 and the association of these two genes with increased BCL2 expression in a non-GCB DLBCL subtype.

Another noticeable finding is that the testicular DLBCL developed from a clone distinct from the soft tissue DLBCL clone. Although most B-cell lymphomas are considered monoclonal, biclonality has been reported on occasion. Sanchez et al. reported that 23 of 477 (4.8%) leukemic B-CLPD cases had ≥2 B-cell clones (6). Compared with monoclonal cases, B-chronic lymphocytic leukemia patients with two or more malignant clones have splenomegaly more frequently and require earlier treatment (6). The presence of two or more B-cell clones is usually suspected based on FCM immunophenotypes and can be confirmed by Southern blot and/or polymerase chain reaction techniques. In most cases, the two B-cell clones will display different surface immunoglobulin light chains or have other phenotypic differences. However, in the present case, immunophenotypes were similar between the soft tissue and testis, which were both positive for CD19, CD20, CD22, CD25, CD79a, and κ-chain. There were, however, slight differences in the expression of CD11c and CD38. The lymphoma cells of the soft tissue and testis were CD11c+CD38- and CD11c-CD38+, respectively; whether or not these differences are meaningful is unclear. In two reported cases of DLBCL harboring two B-cell clones, one clone was CD11c-positive, and the other clone was CD11c-negative (6). Thus, there might have been some association between the CD11c expression and biclonality in DLBCL.

Sanchez et al. also compared two groups of B-CLPD patients: one with two phenotypically distinct B-cell populations and the other with two B-cell populations showing different DNA contents but with a similar immunophenotype (7). The tumors in the group with two distinct populations showed unrelated *IGH* rearrangements, suggesting that they were derived from unrelated B-cell clones, whereas those in the other group were monoclonal and reflective of different stages of evolution from a single clone. In contrast, the present case showed a unique pattern of biclonality: similar immunophenotypes but different karyotypes and heterogeneous configuration of *IGH*. Interestingly, further cytogenetic studies revealed partial trisomy 18q as a common abnormality, and accordingly, both lymphoma cell clones were suspected of being genetically related. Namely, the complex karyotype 47,X,+X,-Y,der(4)t(4;18)(p15;?),del(5)(q?),+13 may have originated from a tumor with trisomy 18 as the primary change, which would be consistent with intraclonal evolution during disease progression. However, the unequivocal presence of different *IGH* rearrangements suggested that the disease in this particular case was due to biclonal malignancy. Partial trisomy 18q might take place as a common possible oncogenic event at a very early stage of differentiation and before *IGH* rearrangements (29). Either way, the present findings underscore the need for intensive cytogenetic analyses as well as immunophenotypic and molecular studies to investigate biclonality in DLBCL.

The authors state that they have no Conflict of Interest (COI).

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