Distinct genetic alterations in Burkitt-like lymphoma with 11q aberration and Burkitt lymphoma: a novel case report of composite lymphoma

Composite lymphoma (CL) is defined as two or more morphologically and immunophenotypically distinct lymphomas within the same tissue site, most of each component has a different clonality accounting for 1-4.7% of all lymphomas. To date, variable components of CL have been reported, such as combination of non-Hodgkin lymphomas (NHL) and Hodgkin lymphoma (HL); multiple B-cell lymphomas, B-cell and T-cell NHL; and complex B-cell, T-cell, and HL. Most reported cases had the co-existence of a B-cell NHL and HL or two distinct B-cell NHL, usually low-grade such as mantle cell lymphoma with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or follicular lymphoma (FL), or FL and CLL/SLL.[1,2] However, CL consisting of large B-cell lymphomas has rarely been reported in the literature.[2,3] Burkitt-like lymphoma with 11q aberration (BLL-11q) is a newly defined subset in the revised 4th edition of World Health Organization (WHO) classification. BLL-11q has been described to resemble BL on morphological, immunophenotypic, and gene expression levels, but lacks *MYC* rearrangements and harbors a chromosome 11q aberration.[4] Although they have overlapping features, co-occurrence of those two lymphomas has not been reported to date. Here, we present a novel case of composite BLL-11q and Burkitt lymphoma (BL) that have distinct morphologic, immunophenotypic, molecular, and genetic features.

A 62-year-old male was referred to the emergency department with a 2-month history of epigastric pain and aggravation. A computed tomography (CT) scan revealed a segmental wall thickening of 5.7 cm in the terminal ileum with encasement of soft-tissue mass-like lesions along the ileocolic vessel, leading to small bowel obstruction. Multiple hypermetabolic lymph nodes in mesentery, paratracheal,

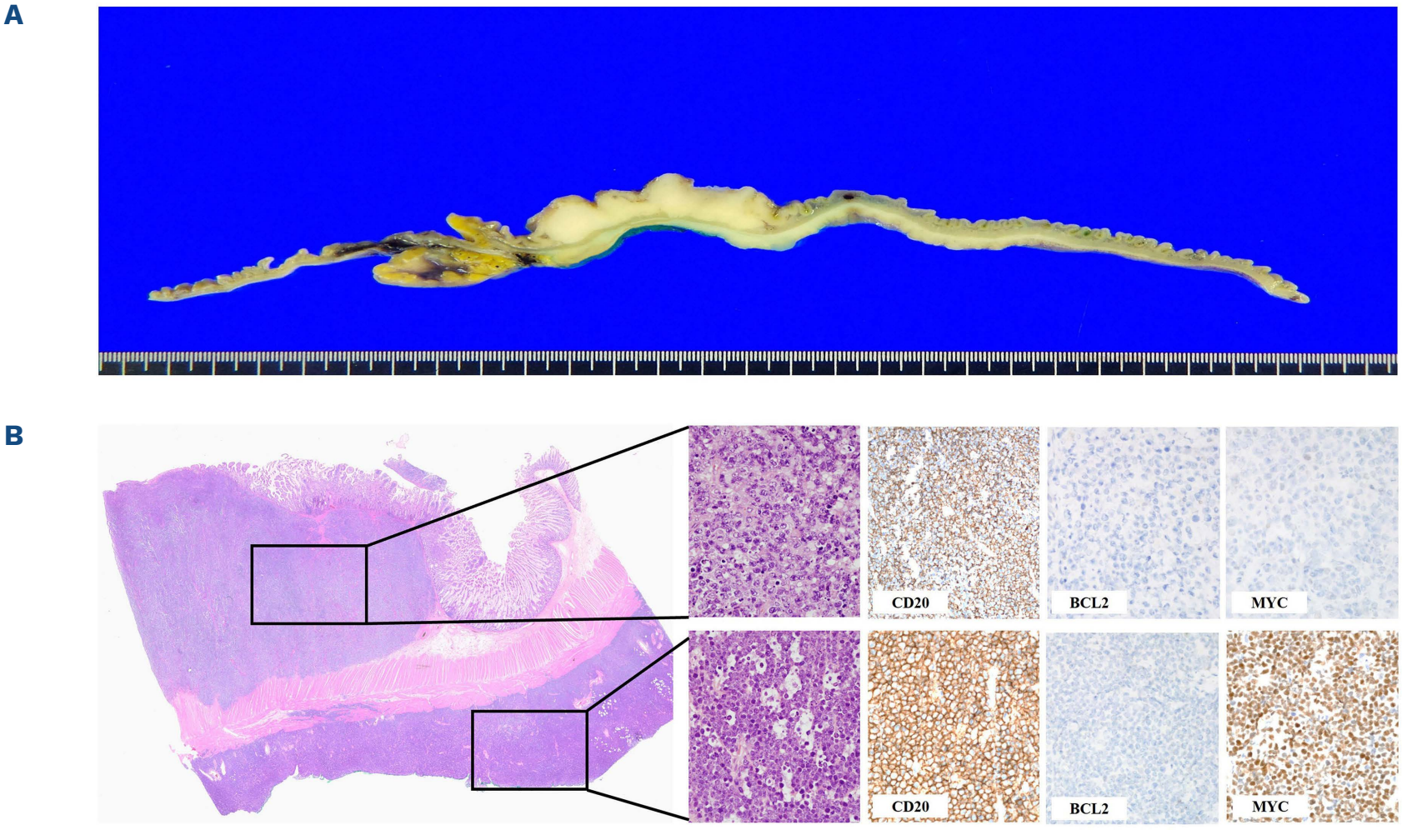
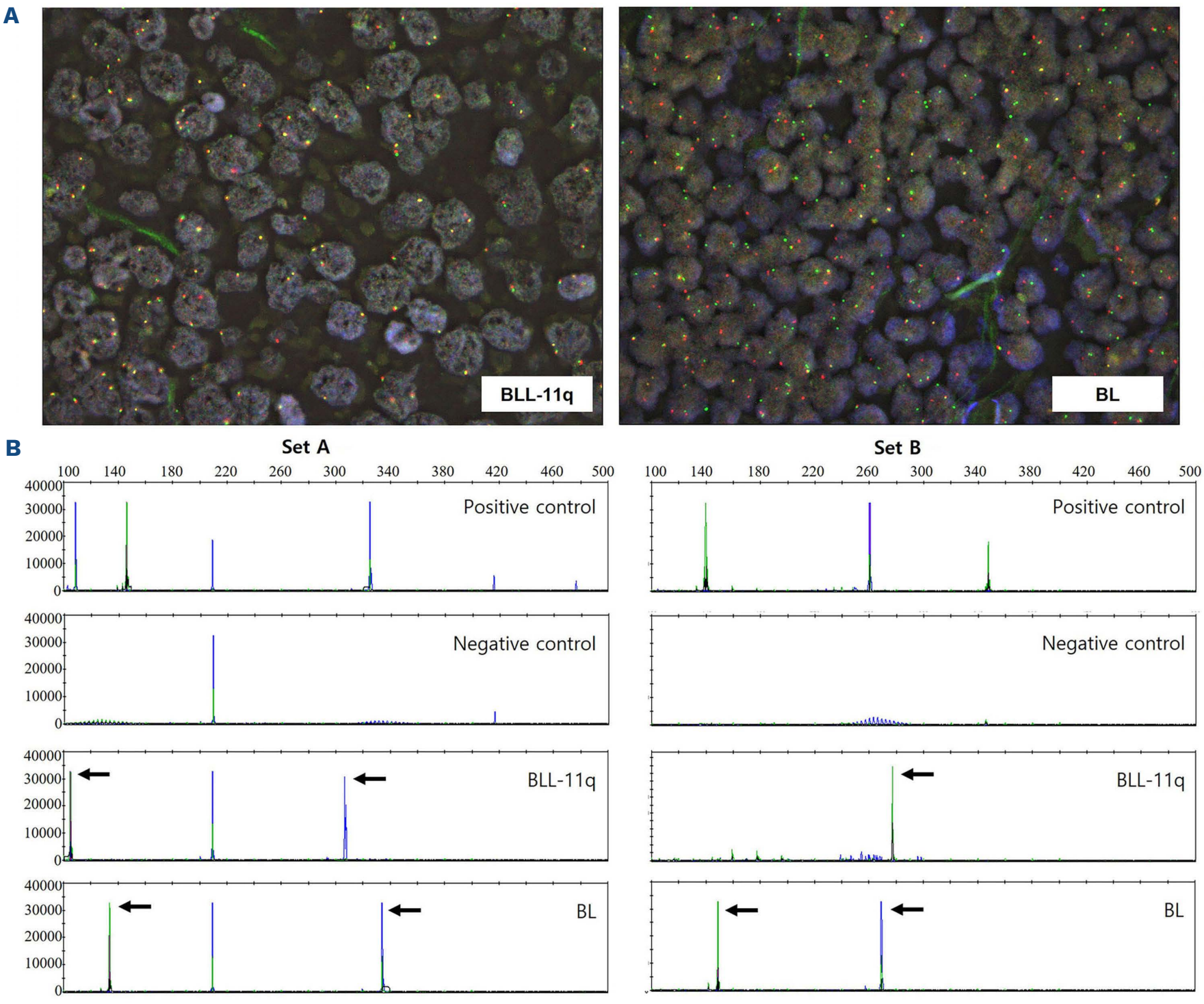


Figure 1. Gross image, histomorphology (haematoxylin and eosin stain) and immunohistochemical staining of composite lymphoma with Burkitt-like lymphoma with 11q aberration and Burkitt lymphoma. (A) Cut surface of a yellow-tan lesion involving the ileal wall along both sides of the muscularis propria. (B) The Burkitt-like lymphoma with 11q aberration (BLL-11q) involving mucosa and submucosa exhibits CD20-positive pleomorphic large lymphoid cells with negativity on BCL2 and MYC. The Burkitt lymphoma (BL) component in subserosa and serosa shows CD20-positive, BCL2-negative, and MYC-positive monomorphic medium size lymphoid cells with starry sky appearance, which are typical findings for BL (×400 magnification).

and pulmonary hilar as well as hypermetabolic bone lesions in clavicle and ischium were detected using positron emission tomography (PET)-CT. The patient had Ann Arbor stage IV, but on a bone marrow biopsy, there was no evidence of involvement of lymphoma. The initial lactate dehydrogenase (LDH) level was increased with 297 IU/L (normal range, 120–250).

A right hemicolectomy was performed as an elective surgery, and an intraluminal fungating mass was observed in the terminal ileum with severe luminal narrowing. The lesion was along both sides of the proper muscle layer consisting of two morphologically distinct components located in the serosal and mucosal layers of the ileum, separately (Figure 1A). The diagnosis of each component was highly suggestive of large cell lymphoma and BL, respectively, based on the histologic findings and immunostaining results. The component of large cell lymphoma showed positivity for CD20, CD10, BCL6 and Ki-67 proliferation index of approximately 90% but negativity for CD5, BCL2, MYC, MUM1/IRF4 and EBER *in situ* hybridization (Figure 1B). Fluorescence *in situ* hybridisation (FISH) analysis was performed with *BCL2*, *BCL6* and *MYC* break-apart rearrangement probes and showed neither rearrangement nor amplification in all three genes in the large cell lymphoma. These findings were suggestive of large B-cell lymphoma with a high probability of diagnosis of diffuse large B-cell lymphoma (DLBCL) at this level. The BL was positive for CD20, MYC, CD10, and BCL6 with Ki-67 proliferation index of over 95% but negative for BCL2, CD5, MUM1/IRF4 and EBER *in situ* hybridization (Figure 1B). 8q24 *MYC* rearrangement by FISH analysis was observed in the BL component (78.3% of all tumor cells) but no rearrangement or amplification was detected in *BCL2* and *BCL6* (Figure 2A). We performed *IgH* gene rearrangement tests on the CL and the two tumor components displayed distinct rearrange-



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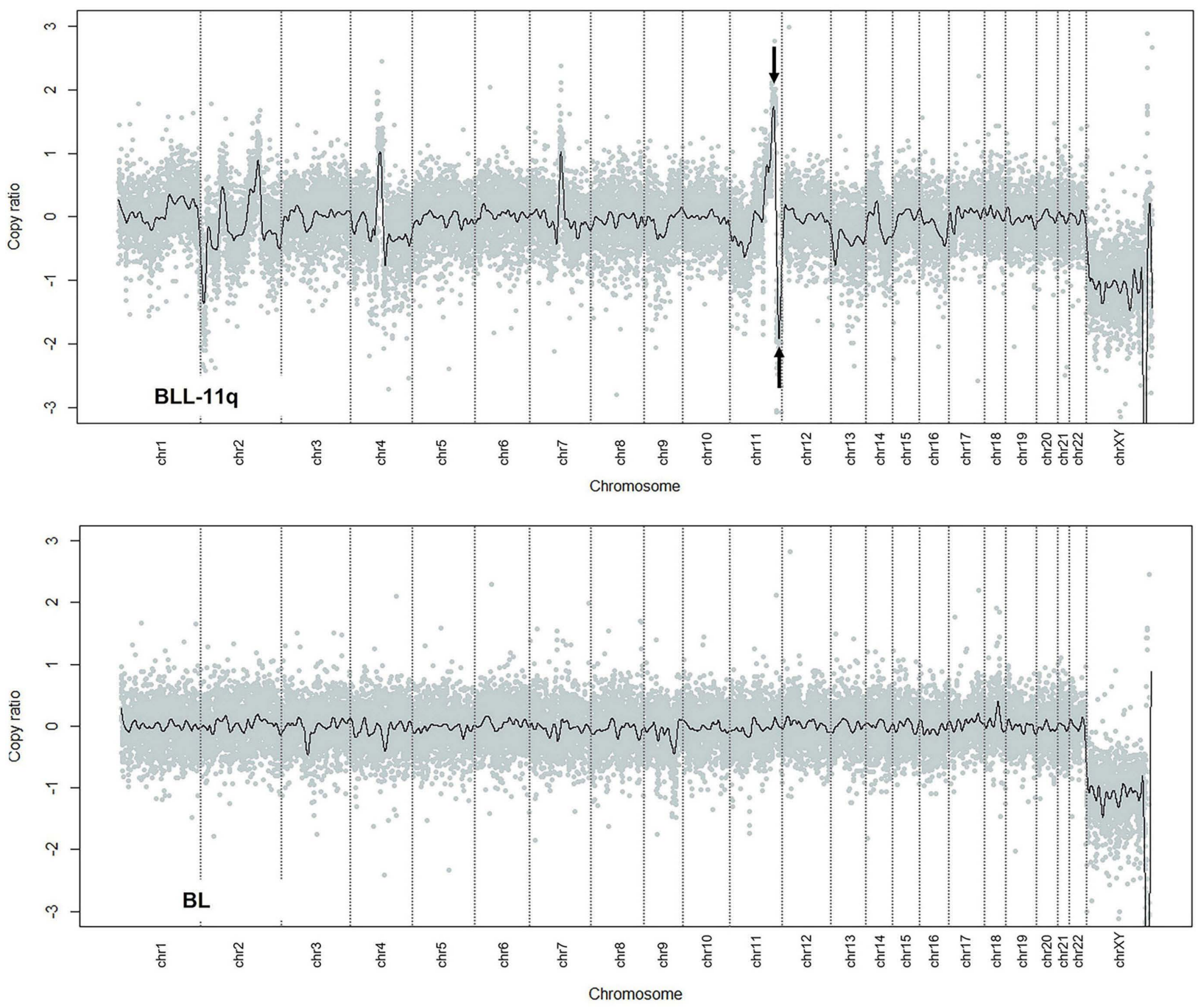

Figure 2. Molecular analyses performed on the composite lymphoma of Burkitt-like lymphoma with 11q aberration and Burkitt lymphoma. (A) On the *MYC* fluorescence *in situ* hybridization (FISH) analysis, the Burkitt-like lymphoma with 11q aberration (BLL-11q) component are negative for *MYC* rearrangement whereas the Burkitt lymphoma (BL) shows *MYC* translocation (78.3% of the tumor cells). (B) Both components showed distinct monoclonality with different sizes of clonal peaks (arrows) on multiplex polymerase chain reaction assay with IGH-A (FR1, FR3, and DH7)) and IGH-B (FR2 and DH) primers. (C) BLL-11q shows gain of 11q23.3 and loss of 11q24.2–24.3 (arrows) but no significant copy number variation is observed in BL.

ment patterns (Figure 2B). The tumor-only targeted next-generation sequencing (NGS) test was performed separately for the two distinct tumor components. The test revealed a distinct pattern of copy number variation (CNV) with an 11q duplication region and terminal deletion on the large B-cell lymphoma component (gain of 11q23.3 and loss of 11q24.2–24.3), which is consistent with that of BLL-11q. In contrast, no significant copy number aberration was noted in the conventional BL component (Figure 2C). The BLL-11q component also exhibited additional gains of 4q22.1 and 7q21.2 and loss of 2p24. The mutations identified through NGS tests are listed in Table 1. A missense mutation of *MYC* (p.P72S), which is known to be pathogenic, was detected in the BL component, whereas it was not identified in the BLL-11q component.[5] Interestingly, these two components exhibited common mutations in *TP53* I195N gene, which is likely oncogenic, and *KMT2D* R5027Q of unknown biologic significance.[6,7]

After the surgery, the patient was treated with a dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-R) regimen. After four cycles, the patient developed disease progression with extensive lymphomatous involvement of abdominal cavity and expired 5 months after initiation of chemotherapy. Four months later, additional excisional biopsy was performed, and the specimen showed Burkittoid morphologic appearance (monomorphic medium-size cells, scanty cytoplasm, fine chromatin with multiple small nucleoli, and “Starry-sky” appearance). It also showed *MYC* rearrangement on FISH analysis but no *BCL2* and *BCL6* which were the similar find-

ings with the BL component of the prior resection specimen. Horing *et al*. reported CL of DLBCL and BL in ileocecal area which was similar site with our case exhibiting two separate clonal population on *IgH* gene rearrangement analysis.[8] Considering that genetic alteration of the case was not fully examined in detail and several cases of BLL-11q have been morphologically indistinguishable from DLBCL, the prior case of CL at the same site may provide a clue for understanding pathogenesis of large B-cell lymphoma.[9,10] Although BLL-11q has been described to resemble BL on morphological, immunophenotypic and gene-expression levels, it lacks *MYC* rearrangements and has a chromosome 11q alteration characterized by proximal gains and telomeric losses: specifically, interstitial gains including a minimal region of gain in 11q23.2–23.3 and losses of 11q24.1–qter.[9,11,12] Recently, Wagener *et al*. have demonstrated that apart from the absence of *MYC* rearrangement and the unique copy number aberration of 11q, BLL-11q lacks genetic mutations in genes of the ID3-TCF3 axis or the SWI/SNF complex such as *ID3*, *MYC*, or *CCND3* that are frequently detected in BL.[11] Gonzalez-Farre *et al.* have shown that BLL-11q has potential driver mutations particularly involving *BTG2*, *DDX3X*, *ETS1*, *EP300*, and *GNA13* but *ID3*, *TCF3*, or *CCND3* mutations are absent, suggesting that BLL-11q is a germinal center-derived and closer to high-grade B-cell lymphoma or diffuse large B-cell lymphoma (DLBCL) than to BL.[10]

In line with those studies, we demonstrated distinct histologic and genetic features between the BL and BLL-11q components, particularly as the form of CL. The BLL-11q component had a gain of 11q23.3 and loss of 11q24.2–24.3 and there were no gains of 1q, 2p16.1 or 7p or loss of 1p36.32 that are usually observed in BL or germinal center B-cell (GCB) like-DLBCL. In addition, we could not detect any significant CNV in the BL component.[10,13] Distinct mutation profiles were also observed between the two components in that BL harbored *MYC* missense mutation, but BLL-11q did not. Thus, it is likely that BLL-11q is a separate entity from BL; it is also noteworthy that those distinct entities can exhibit the development of a composite neoplasm.

The BLL-11q component was CD10/BCL6-positive and MUM1-negative, highly suggestive of GCB derivation. Intriguingly, it showed several common mutations in *TP53*, *PDCD11*, *KMT2D*, and *DDX3X* with the BL component. Those mutations have been reported more frequently in BL or GCB B-cell lymphoma than in non-GCB type lymphomas, although the prevalence of *KMT2D* mutation is not significantly different between GCB-derived and non-GCB B-cell lymphomas.[10,14,15] These findings suggest that both components might originate from a common precursor of GCB cell, then diverge before the clonal expansion. In this respect, it can be hypothesized that identically detected mutations of *TP53*, *PDCD11*, and *KMT2D* in both components might occur in early B-cell differentiation during lymphomagenesis before the divergence, and subsequently show distinct clonal evolution including *IgH* gene rearrangement, copy number aberration, and *MYC* gene rearrangement. Nevertheless, the possibility that the mutations shared with two components were germline alterations, or that the same mutations occurred

Table 1. Mutations identified in composite lymphoma of Burkitt-like lymphoma with 11q aberration and Burkitt lymphoma.

Type	Nucleotide Changes	Amino Acid Changes	Variant ID
BLL-11q			
BRCA2	c.623T>G	p.V208G	rs80358865
PDCD11	c.2875C>G	p.L959V	rs568839783
KMT2D	c.15080G>A	p.R5027Q	rs774403945
TP53	c.584T>A	p.I195N	-
DDX3X	c.676A>C	p.T226P	-
PHF6	c.374G>C	p.X125_splice	-
BL			
BRCA2	c.623T>G	p.V208G	rs80358865
MYC	c.214C>T	p.P72S	rs28933407
MYC	c.223C>G	p.P75A	-
PDCD11	c.2875C>G	p.L959V	rs568839783
KMT2D	c.15080G>A	p.R5027Q	rs774403945
TP53	c.584T>A	p.I195N	-
P2RY8	c.800_840del	p.Y267Sfs*62	-
DDX3X	c.488A>G	p.Y163C	-

BLL-11q: Burkitt-like lymphoma with 11q aberration; BL: Burkitt lymphoma.

by chance in two different progenitors of the lymphoma components, cannot be completely ruled out.
In conclusion, we reported a novel case of CL with BLL-11q and BL in which the components had distinct *IgH* rearrangement patterns and different features on morphologic, immunophenotypic, and genetic levels. Although multiple cases of CL with variable combinations have been reported, there have been few cases consisting of clonally unrelated and aggressive B-cell lymphomas. Considering that categorization of BLL-11q as a variant of BL, DLBCL or another distinct form of large B-cell lymphoma remains uncertain, the present case is significant in keeping with previous reports in terms of supporting the perspective that BLL-11q is a distinct entity from BL.[8,12] This sheds light on the lymphomagenesis of CL that may originate from non-immunoglobulin gene-rearranged common progenitor cells.

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Disclosures

No conflicts of interest to disclose.

Contributions

MK and HG performed the histological examination of the case and MK wrote the first draft of the manuscript with support from HSH. SC and DHY provided material or data of the case. MK, HSH and HG analyzed and interpretated data. HG supervised the work. All authors approved the submission of the manuscript.

Data-sharing statement

Data available on request from the authors.

References

1. Goyal G, Nguyen AH, Kendric K, Caponetti GC. Composite lymphoma with diffuse large B-cell lymphoma and classical Hodgkin lymphoma components: a case report and review of the literature. Pathol Res Pract. 2016;212(12):1179-1190.
2. Kuppers R, Duhrsen U, Hansmann ML. Pathogenesis, diagnosis, and treatment of composite lymphomas. Lancet Oncol. 2014;15(10):e435-446.
3. Miyaoka M, Kikuchi T, Carreras J, et al. Composite follicular lymphoma and CD5-positive nodal marginal zone lymphoma. J Clin Exp Hematop. 2016;56(1):55-58.
4. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Revised 4th edition. Lyon: International Agency for Research on Cancer, 2017.
5. Sati AOM, Osman WA, Ahmedon EAM, et al. Single nucleotide polymorphisms of the c-MYC gene's relationship with formation of Burkitt's lymphoma using bioinformatics analysis. bioRxiv. 2018 Oct 24. doi:10.1101/450783. [preprint, not peer-reviewed]
6. Testoni M, Zucca E, Young KH, Bertoni F. Genetic lesions in diffuse large B-cell lymphomas. Ann Oncol. 2015;26(6):1069-1080.
7. Zenz T, Kreuz M, Fuge M, et al. TP53 mutation and survival in aggressive B cell lymphoma. Int J Cancer. 2017;141(7):1381-1388.
8. Horing E, Staiger AM, Lenze D, et al. Burkitt lymphoma and diffuse large B-cell lymphoma: a unique case of a composite lymphoma of different clonal origin. Leuk Lymphoma. 2018;59(1):249-252.
9. Salaverria I, Martin-Guerrero I, Wagener R, et al. A recurrent 11q aberration pattern characterizes a subset of MYC-negative high-grade B-cell lymphomas resembling Burkitt lymphoma. Blood. 2014;123(8):1187-1198.
10. Gonzalez-Farre B, Ramis-Zaldivar JE, Salmeron-Villalobos J, et al. Burkitt-like lymphoma with 11q aberration: a germinal center-derived lymphoma genetically unrelated to Burkitt lymphoma. Haematologica. 2019;104(9):1822.
11. Wagener R, Seufert J, Raimondi F, et al. The mutational landscape of Burkitt-like lymphoma with 11q aberration is distinct from that of Burkitt lymphoma. Blood. 2019;133(9):962-966.
12. Grygalewicz B, Woroniecka R, Rymkiewicz G, et al. The 11q-gain/loss Aberration occurs recurrently in MYC-negative Burkitt-like lymphoma with 11q aberration, as well as MYC-positive Burkitt lymphoma and MYC-positive high-grade B-cell lymphoma, NOS. Am J Clin Pathol. 2017;149(1):17-28.
13. Boerma EG, Siebert R, Kluin PM, Baudis M. Translocations involving 8q24 in Burkitt lymphoma and other malignant lymphomas: a historical review of cytogenetics in the light of todays knowledge. Leukemia. 2009;23(2):225-234.
14. Schmitz R, Young RM, Ceribelli M, et al. Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics. Nature. 2012;490(7418):116-120.
15. Dubois S, Viailly P-J, Mareschal S, et al. Next-generation sequencing in diffuse large B-cell lymphoma highlights molecular divergence and therapeutic opportunities: a LYSA study. Clin Cancer Res. 2016;22(12):2919-2928.