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Burkitt-like lymphoma with 11q aberration

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Burkitt-like lymphoma with 11q aberration (BLL-11q) is a new provisional entity in the revised 2016 WHO classification of hematopoietic and lymphoid tumors.¹ It refers to a subset of high-grade B-cell lymphomas that resemble Burkitt lymphoma with similar morphology, phenotype, and gene expression profiling, but lack *MYC* gene rearrangements. Instead, these lymphomas carry chromosome 11q proximal gains and telomeric losses, suggesting co-dysregulation of oncogenes and tumor suppressor genes.

Here, we report a case of Burkitt-like lymphoma with 11q aberration. We contribute to further characterize this rare entity with molecular genomic and clinicopathological features.

Case presentation and history. The patient was a 23-year-old male who

presented with rapidly growing nasopharyngeal mass. He denied recent history of fevers, chills, nausea, vomiting, or weight loss. F18-FDG PET/CT scan demonstrated intensely hypermetabolic nasopharyngeal and splenic masses and a left level IIIb lymph node. Therefore, the patient underwent nasopharyngeal tissue biopsy.

Results. The H&E sections of the nasopharyngeal mass showed sheets of monomorphic atypical lymphoid infiltrate composed of medium-sized lymphocytes with round nuclei, vesicular chromatin, and inconspicuous nucleoli. Atypical mitotic figures and apoptotic bodies were easily appreciated. Scattered histiocytes in the background rendering starry-sky appearance were noted (Fig. 1). The morphologic features raised the possibility of Burkitt lymphoma or Burkitt-like lymphoma. By immunohistochemistry, the atypical lymphoid infiltrates were diffusely positive for B cell markers (CD20 and PAX-5) with coexpression of CD10 and Bcl-6, and were negative for CD5, Bcl-2, CD30, CD34, c-MYC, EBER, and TdT. The tumor cells showed very high proliferation index with approximately 100 percent of cells positive for Ki-67 (Fig. 2, next page).

Cytogenetic analysis

revealed abnormal clone of 48, XY, +X, ?der(11)t(1;11)(q25;q24),+12 (Fig. 3, next page). FISH studies were negative for *MYC*, *BCL2*, or *BCL6* rearrangements (Fig. 4, page 3). To further characterize this tumor, we performed next-generation sequencing using our institutional 1,385-gene panel (gene list at www.utsouthwestern.edu/sites/genomics-molecular-pathology/assets/utsw-informatics-ngs-gene-list-for-web-site-20180807.pdf). NGS confirmed the presence of chromosome 11q gain/loss in the copy number alterations plot (Fig. 5, page 3) and detected likely pathogenic hotspot variants in the following genes: *EZH2*, *KMT2D*, and *ERCC2* (Table 1, next page). No mutations in *MYC*, *FLI1*, *USP2*, *CBL*, and *ETS1* genes were detected. Overall, the combined morphologic, immunohistochemical, and cytogenetic findings were consistent with Burkitt-like lymphoma with 11q aberration.

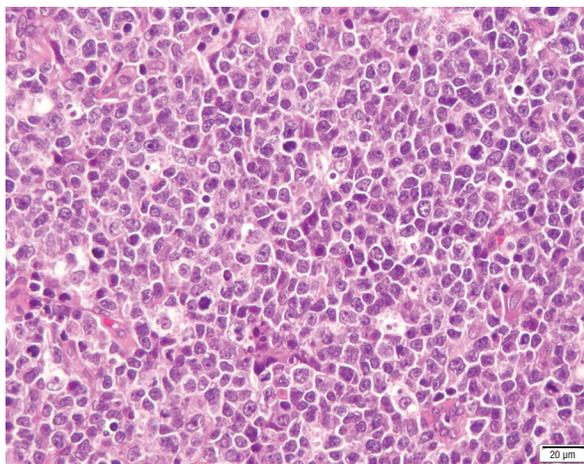


Fig. 1. H&E-stained section of the nasopharyngeal mass showing sheets of medium- to large-sized atypical lymphoid infiltrate with starry-sky pattern.

Table 1. Mutations identified in the lymphoma sample by NGS

Gene	Coding notation	Amino acid change	Aberration type	Variant allele frequency
<i>EZH2</i>	c.1920A>G	p.Tyr646Ser	Missense mutation	24.9%
<i>KMT2D</i>	c.4135_4136delAT	p.Met1379fs	Frameshift	36.8%
<i>ERCC2</i>	c.594+2_594+5delTGAG		Splice donor variant	45.9%

The patient was then treated with six cycles of dose-adjusted EPOCH (etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone) plus rituximab (DA-EPOCH-R) with prophylactic intrathecal methotrexate. Surveillance PET scan done three months after completing DA-EPOCH-R showed complete remission. The patient is currently doing well with no specific complaints.

Discussion. Burkitt lymphoma is a type of aggressive B-cell lymphoma derived from germinal center B cells. The molecular hallmark of Burkitt lymphoma is the translocation of the *MYC* gene. It has been controversial whether Burkitt lymphoma without *MYC* translocation truly exists. The lymphomas with morphological features typical for Burkitt lymphoma but lacking *MYC* rearrangements were previously classified as atypical Burkitt/Burkitt-like lymphoma.² Pienkowska-Grela, et al., first reported four *MYC*-negative Burkitt lymphoma cases with recurrent genetic abnormality within chromosome 11.³ It was then reported that *MYC*-negative Burkitt lymphoma and Burkitt-like lymphoma carry a peculiar pattern of chromosome 11q aberration characterized by interstitial gains including 11q23.2-q23.3 and telomeric losses of 11q24.1-qter.⁴ Of note, lymphomas with the typical 11q-gain/loss pattern seem to have more frequent nodal presentation than Burkitt lymphoma, and they are mainly found in children and young adults (younger than 40 years).⁴ These lymphomas have complex karyotypes compared with Burkitt lymphoma and happen particularly often in post-transplant settings.^{5,6} These *MYC*-negative lymphomas were recognized as a new provisional entity, “Burkitt-like lymphoma with 11q aberration,” in the 2016 WHO classification because its precise taxonomy is still controversial.¹ A recent study demonstrated that most patients with BLL-11q have favorable treatment outcomes, although opti-

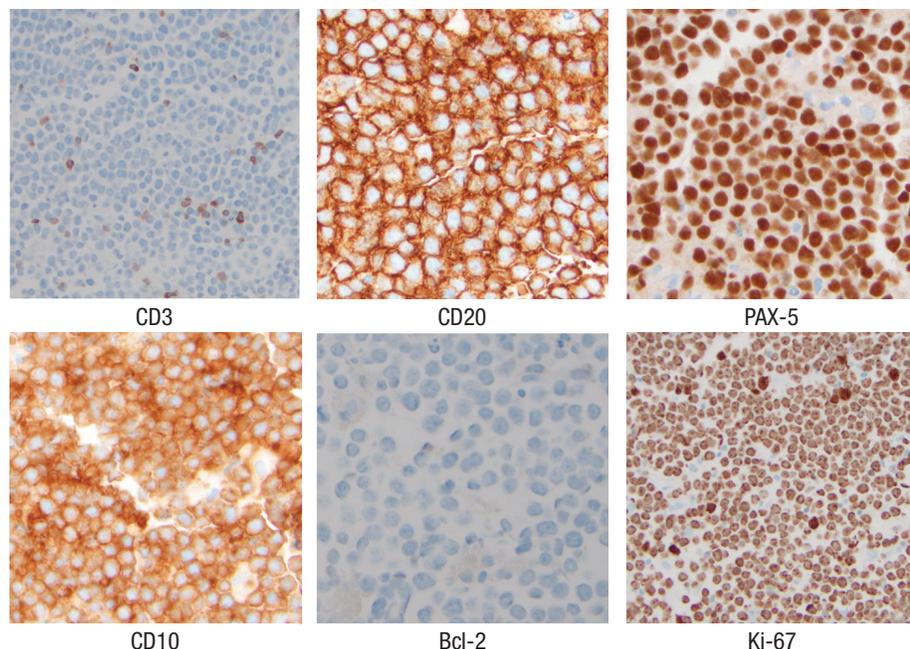


Fig. 2. Immunohistochemistry showing lymphoma cells expressing CD20, PAX-5, and CD10, and negative for CD3 and Bcl-2. Ki-67 demonstrating high proliferation index of nearly 100 percent.

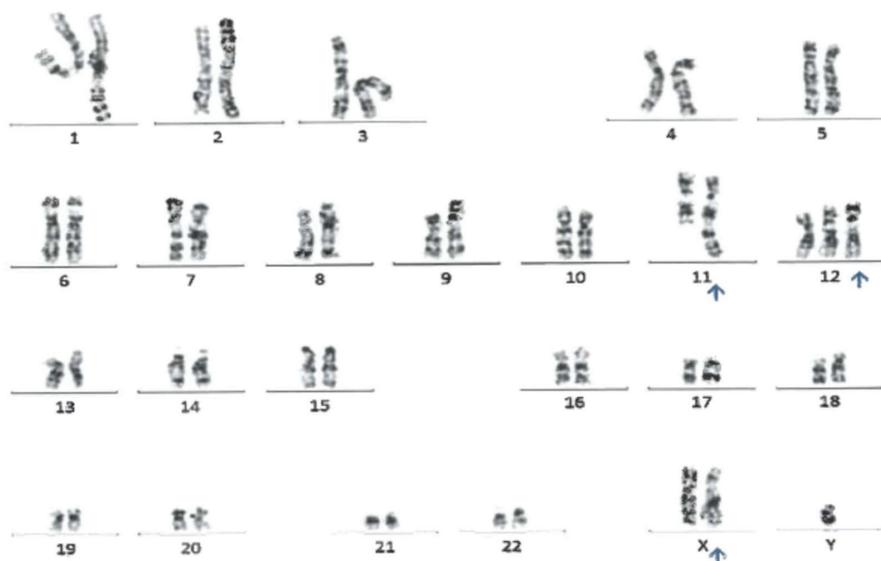


Fig. 3. Cyto-genetic analysis showing a complex karyotype: 48, XY, +X, ?der(11)t(1;11)(q25;q24),+12.

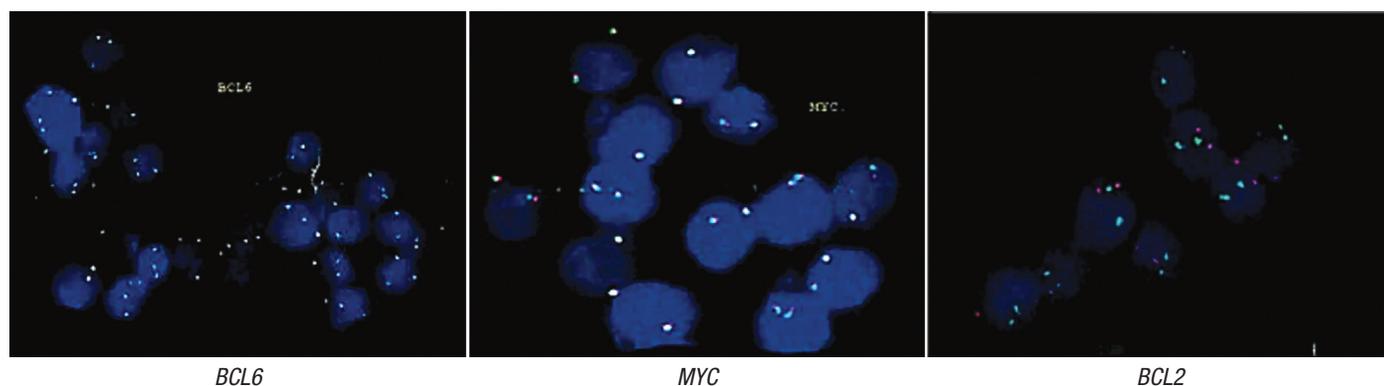


Fig. 4. Intact *BCL6*, *MYC*, and *BCL2* genes by FISH.

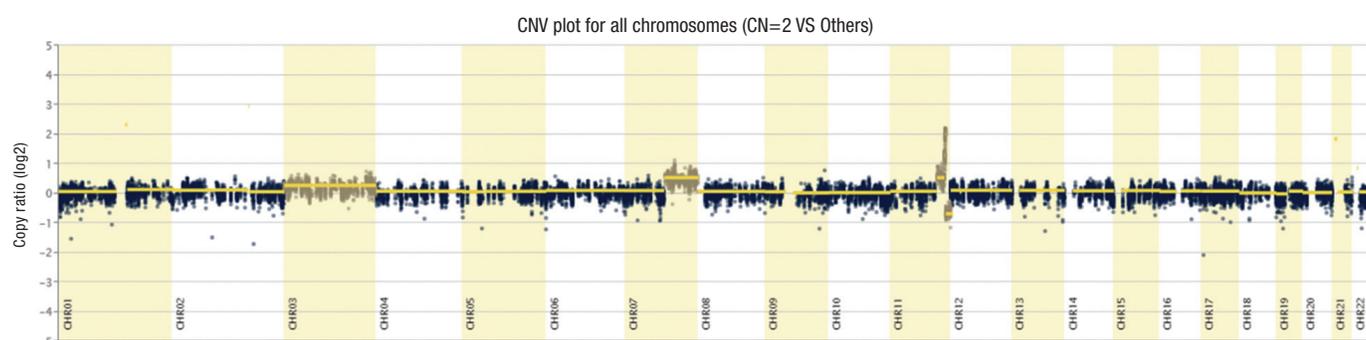


Fig. 5. Copy number variation was assessed using CNVkit software.

mal clinical management remains to be determined.⁷

Our case confirms that BLL-11q usually shows complex karyotypes and has lower levels of *MYC* expression compared with Burkitt lymphoma. The NGS test confirmed the copy number gain of oncogenes *PAFAH1B2* and *CBL* in the q11q23.3 region and the loss of genes *ETS1* and *FLII* in the 11q24 region, similar to the previous report.⁴ The specific features of BLL with 11q aberration raise the question of whether these lymphomas truly belong to the entity of Burkitt lymphoma or should be considered as another set of high-grade B-cell lymphomas with similar features.⁴

Furthermore, using NGS, we identified additional genomic alterations in this case, including gain-of-function activating mutation in *EZH2*, loss-of-function frameshift in *KMT2D*, and splicing site variant in

ERCC2. Notably, *EZH2* and *KMT2D* mutations have been reported to be germinal center B cell-specific oncogenic events in lymphomas.^{8,9} These findings can help us better understand the pathogenesis of this rare entity and identify potential therapeutic targets. For instance, lymphomas harboring *EZH2* and *KMT2D* mutations have been reported to be sensitive to *EZH2* inhibitors and HDAC inhibitors, respectively.^{10,11} With only a limited number of cases reported, further studies are needed to fully understand the significance of these genomic alterations and define the clinical course of this rare entity. □

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Test yourself

Here are three questions taken from the case report. Answers are online now at www.amp.org/casereports and will be published next month in CAP TODAY.

- 1.** Which of the following statements is true regarding Burkitt-like lymphoma with 11q aberration?
 - a.** It refers to a subset of lymphomas that resemble Burkitt lymphoma but lack *MYC* translocation.
 - b.** It has a chromosome 11q alteration characterized by proximal gains and telomeric losses.
 - c.** It usually harbors complex karyotype.
 - d.** All of the above

- 2.** What types of cells are Burkitt lymphoma and Burkitt-like lymphoma derived from?
 - a.** Mature B cells of unknown type;
 - b.** Pre-germinal center B cells
 - c.** Germinal center B cells;
 - d.** Post-germinal center B cells

- 3.** Which of the following ancillary techniques can be used in the diagnosis of Burkitt-like lymphoma with 11q aberration?
 - a.** Fluorescence in situ hybridization (FISH)
 - b.** Array comparative genomic hybridization (aCGH)
 - c.** Next-generation sequencing
 - d.** All of the above
 - e.** None of the above