Case Report: Burkitt Lymphoma with Dual Translocation of Chromosome 14: A Novel Chromosomal Abnormality of t(8;14),t(14;15)

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Abstract. Burkitt lymphomas (BLs) frequently show secondary chromosomal abnormalities. Here, the authors describe a case of BL with an unusual dual translocation of chromosome 14, t(8;14) and t(14;15), and partial duplication of 1q. This 5-yr-old female patient had several unfavorable prognostic factors including elevated serum lactate dehydrogenase activity and involvement of the central nervous system and bone marrow. Despite receiving CCG-106A chemotherapy, she was resistant to therapy and died on the 70th hospital day. To our knowledge, this is the first documented case report of BL harboring dual translocation of chromosome 14 involving chromosomes 8 and 15, which may be a factor associated with unfavorable clinical course.

Keywords: Burkitt lymphoma, cytogenetics, chromosome 14, dual translocation t(8;14),t(14;15)

Introduction

Burkitt lymphoma (BL), a highly aggressive lymphoma, is defined by distinct histopathological morphologies and cytogenetic abnormalities involving the MYC gene [1]. The MYC gene is usually translocated to the immunoglobulin heavy-chain gene on chromosome 14 resulting in t(8;14)(q24;q32) and is less commonly translocated to light-chain genes on chromosome 2 and 22 resulting in t(2;8)(p12;q24) and t(8;22)(q24;q11), respectively [2]. Although abnormality of the MYC gene is known to be an essential event in tumorigenesis of BL, its prognostic relevance is still unclear. Secondary cytogenetic abnormalities are considered to have adverse prognostic implications [3-10]. Previous reports have documented secondary chromosomal abnormalities affecting chromosome 14 in BL [7,11]. However dual translocation of chromosome 14 is a very rare event. Most of the reported cases have demonstrated t(8;14) and t(14;18) in non-Burkitt B cell malignancies [12-14]. To our knowledge, only one case of BL with t(8;14) and t(14;18) has been reported in English [15]. We now report the first case of BL with t(14;15) as a secondary chromosomal abnormality resulting in dual translocation of chromosome 14.

Case Report

A 5-yr-old female patient came to our hospital for the evaluation of headache and gait disturbance of 2 weeks duration. On initial laboratory tests, her complete blood count (CBC) revealed hemoglobin 8.4 g/dL, platelets 116 × 10^9/L, and white blood cells 3.9 × 10^9/L comprised of myelocytes 2%, metamyelocytes 2%, neutrophils 38%, lymphocytes 50%, monocytes 5%, and eosinophils 3%. Serum lactate dehydrogenase (LDH) activity was 1392...
IU/L (reference range: 180–460). Bone marrow aspiration and biopsy showed markedly increased marrow cellularity (100%) with predominant lymphoid cells. Radiological studies including MRI and CT of the head and neck demonstrated a huge ill-defined mass involving bilateral paranasal sinuses with mandibular bone destruction. Tissue sections from the mass showed diffuse infiltration of medium-sized lymphoid cells with brisk mitotic activity. On immunohistochemical staining, the tumor cells were positive for LCA, CD10, and CD20 and negative for CD3, CD23, CD56, bcl-2, and Tdt. The Ki-67 labeling index was 99%.

Karyotype analysis was performed on bone marrow cells using standard methods. Following cell culture for 24 hr, cells were prepared for cytogenetic analysis using the standard colcemid, hypotonic, and fixation technique. After G-banding using a conventional trypsin-Giemsa technique, cytogenetic findings were described according to the guidelines of International System for Human Cytogenetic Nomenclature (ISCN 2005).

G-banded chromosomes revealed the following karyotype: 46,XX,t(8;14)(q24.1;q32),t(14;15)(q32;q15)[2]/46,idem,dup(1)(q12q32)[18] (Fig. 1). Fluorescence in situ hybridization (FISH) was performed using the LSI IGH dual color break apart rearrangement probe (Vysis, Stuttgart, Germany), designed to detect chromosomal breakage at J or switch region in the immunoglobulin heavy chain locus (14q32). The FISH analysis in combination with G-banding demonstrated two orange signals orthotopically residing in chromosome 14 and two separate green signals translocated on different chromosomes corresponding to 8 and 15, which represented a dual translocation of t(8;14) and t(14;15) (Fig. 2, page 78).

On the 8th hospital day (HD), chemotherapy was started according to Children’s Cancer Group protocol 106A, but failed to elicit a remarkable response. On follow-up, the patient showed severe neutropenia (<0.5 × 10⁹/L) on the 20th HD (12th day after starting chemotherapy) and spontaneous bleeding on the 52th HD. Finally the patient succumbed to sepsis, pulmonary hemorrhage, and pneumonia on the 70th HD.

Discussion

Abnormality of the MYC gene is associated with virtually all cases of BL and is known to be essential for the initial tumorigenic process. However, other chromosomal abnormalities are also frequently observed in BL. Sporadic cases of BL usually show more complex chromosomal abnormalities than Epstein-Barr virus (EBV)-positive endemic BL, and karyotype complexity may be related to unfavorable tumor progression or therapeutic response in BLs [9,10,12,16]. The present case showed complex chromosomal abnormalities involving chromosome 1, 8, 14, and 15. Among them, the t(8;14) abnormality and the partial duplication of 1q are not unusual in BLs, but t(14;15) is unique to the present case. Although it is unclear whether the cytogenetic abnormality involving chromosome 15q has a positive role in BL tumorigenesis, the 15q15 region contains several candidate genes, including one confirmed gene INOC1 (INO80 complex homolog 1) and 20 validated genes [17]. The mutation of INOC1 gene has been reported to be related to hypersensitivity to agents that cause DNA damage and transcriptional defects [18]. CKMT1B (creatine kinase mitochondrial 1B) gene, one of the validated genes, has been reported to contribute to cancer cell survival and poor prognosis in several cancers [17]. Heerema et al [19] suggested that genes of 15q13-15 may be involved in leukemogenesis in pediatric acute lymphoblastic leukemia (ALL- L1, L2). Chromosomal aberrations involving 15q15 have been found in ALL, chronic lymphocytic leukemia, diffuse large B-cell lymphoma, and liposarcoma [20-23]. These reports support the possibility that some genes located in 15q15 are related to lymphoid malignancies.

The present case followed a rapidly progressive clinical course without response to therapy; the patient died of severe neutropenia and associated complications. Lones et al [10] and Garcia et al [16] suggested that abnormalities of the long arm of chromosome 1 are associated with a poor outcome in BL. In addition to the partial duplication of 1q, the present case presented some known poor prognostic factors, which included elevated serum LDH activity, central nervous system involvement,
Fig. 1. G-banded karyotyping of bone marrow cells showed 46,XX,t(8;14)(q24.1;q32),t(14;15)(q32;q22)(A) and partial karyotype dup(1)(q12q32),t(8;14)(q24.1;q32),t(14;15)(q32;q22)(B). The arrows indicate affected chromosomes.
bone marrow involvement, and complex chromosomal abnormalities. It is plausible that the alteration of 15q may adversely affect tumorigenesis and clinical behavior in BL.

The authors describe the first case of BL with t(14;15) in combination with t(8;14) resulting in dual translocation of chromosome 14 and partial duplication of 1q; the tumor followed an aggressive clinical course.

References


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