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Burkitt Leukemia With Precursor B-Cell Immunophenotype and Dual Translocation of t(14;18) and t(8;14) in a Child: Case Report and Review of the Literature

Işık Odaman Al, MD, Cengiz Bayram, MD,* Başak Koç, MD,* Gizem Ersoy, MD,* Ezgi Paslı Uysalol, MD,* Hilal Akı, MD,† and Gül Nihal Özdemir, MD**

Background: Burkitt leukemia (BL) with the precursor B-cell immunophenotype is a rarely reported condition. The prognosis of such patients is similar to that of classic BL. However, the combination of chromosomal translocations associated with *bcl-2* and *c-myc* rearrangement has a poor prognosis.

Observations: An 11-year-old child presented with fever and weakness. Bone marrow aspiration showed morphologically L1 type blasts and flow cytometry analysis was compatible with precursor B-cell immunophenotype. Cytogenetic analysis revealed a combination of t(8;14) and t(14;l8).

Conclusions: The combination of t(8;14) and t(14;l8) can exhibit different immunophenotypical and morphologic features in leukemias.

Key Words: Burkitt leukemia, ımmunophenotype, t(8;14)

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Burkitt leukemia (BL) accounts for 2% of all cases of childhood acute lymphoblastic leukemia (ALL). BL is diagnosed based on morphologic, immunophenotypical, and cytogenetic findings. Morphologically, BL cells often exhibit FAB L3 type blasts and typically carry t(8;14), t(2,8), and t(8;22) involving the *MYC* oncogene. Chromosomal rearrangement of the *MYC* gene is the characteristic cytogenetic anomaly of BL and plays a key role in the pathogenesis and progression of the disease. The most common cytogenetic anomaly associated with BL is t(8;14). Immunophenotypical investigation shows CD10, CD19, CD20, CD22, and surface immunoglobulin positivity, whereas precursor B-cell markers such as TdT and CD34 are negative.[1] Rare cases of BL with TdT and CD34 positivity and the precursor B-cell immunophenotype have been reported.[1–5]

Herein, we describe a BL patient with unusual features. The difficulties encountered in this unique case during diagnosis, classification, and treatment are discussed.

CASE

An 11-year-old child presented with fever and weakness. A diffuse petechial rash and hepatosplenomegaly were noted on physical examination. Full blood count findings were as follows: white blood cell count, 36,600/mm^3; hemoglobin, 10 g/dL; hematocrit, 29%; platelet count, 17,000/mm^3. Lymphoblasts were detected on peripheral blood smear. Biochemical investigation showed a high uric acid (17 mg/dL) and lactate dehydrogenase (LDH) (2965 U/L) levels. Liver and renal function tests were normal. The LDH level increased to 12,000 U/L at follow-up. Bone marrow aspiration showed morphologically L1 type blasts (Fig. 1). Flow cytometry revealed a blast rate of 84% (5% CD3, 3% CD5, 4% CD7, 2% CD13, 0.4% CD33, 0.1% CD64, 93.4% CD22, 94% CD10, 93.9% CD19, 11% CD20, 0.6% CD34, 6% CD117, 2% MPO, and 58.7% TdT) and surface immunoglobulin (κ and λ) negativity. On the basis of flow cytometry and morphology findings, the patient was diagnosed as precursor B-cell ALL. Chemotherapy was started according to the ALL-IC 2009 protocol. The leukocyte count and uric acid level decreased in response to steroid; however, treatment was complicated by pancreatitis. In addition, t(12;21), t(1;19), t(4;11), and t(9;22), which were analyzed by using polymerase chain reaction technique, were all negative. He was steroid resistant according to the eighth day of blood smear. Bone marrow aspiration at day 15 showed 60% blasts (M3 BFM classification) and 53.8% minimal residual disease, and thus the patient was reclassified as high-risk group according to the assessments done on day 8 and on day 15 of chemotherapy, based on ALL-IC 2009 protocol risk group stratification. On day 18 of ALL therapy, the results of karyotype investigation performed at the time of diagnosis by G-banding showed that t(8;14) and t(14;18) were positive. The full karyotype was 46,XY, t(8;14)(q24;q32), t(14;18)(q32;q21). t(8;14) was repeated in a peripheral blood sample via the fluorescence in situ hybridization (FISH) method for the confirmation and was found to be positive by 34%. Positron emission tomography did not show a mass lesion. The treatment was changed to BL

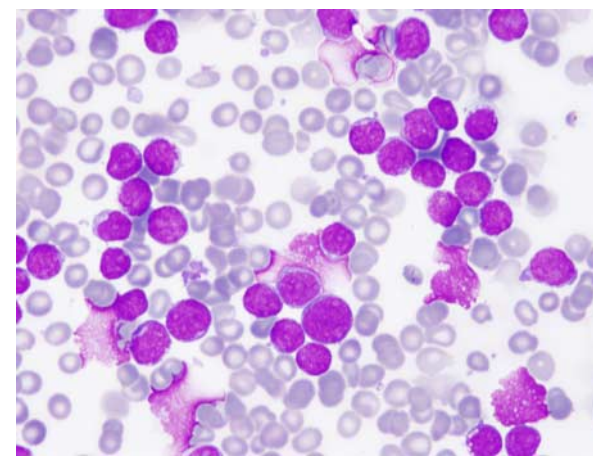

FIGURE 1. The morphology of the marrow blast cells was compatible with acute lymphoblastic leukemia, FAB L1 subtype. full color online

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From the *Department of Pediatric Hematology and Oncology, Kanuni Sultan Suleyman Education and Research Hospital; and †Department of Pathology, Cerrahpaşa Faculty of Medicine, Istanbul University, Istanbul, Turkey.
The authors declare no conflict of interest.
Reprints: Işık Odaman Al, MD, Department of Pediatric Hematology and Oncology, İstanbul Kanuni Sultan Süleyman Education and Research Hospital, İstanbul 34303, Turkey (e-mail: dr.odamanal@gmail.com).
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TABLE 1. Clinical Findings of 3 Pediatric Patients With Concurrent t(14;18) and *8q24/c-MYC* Rearrangement

Case	Age (y)	Sex	Phenotype	TdT	CD10	CD19	CD20	sIg M	Cytogenetics	OS (mo)	References
1	15	Male	FAB L2	+	+	+	−	−	t (14;18) t (8;14)	4 Dead	15
2	15	Female	NA	+	+	+	+	+	t (14;18) t (8;9)	53 Alive	20
3	11	Male	FAB L1	+	+	+	−	−	t (14;18) t (8;14)	8 Dead	Present study

NA indicates not available; OS, overall survival; Slg, surface immunoglobulin; Tdt, terminal deoxynucleotidyl transferase.

BFM NHL 2004 protocol. After the first cycle of chemotherapy protocol, blast rate was <5% in the bone marrow examination via morphologic and flow cytometry analysis and remission was achieved. The patient completed the chemotherapy protocol without complication and remission was sustained. Ten days after the completion of chemotherapy, the leukocyte count was found to be 109,000/mm^3 at following visit. Biochemical findings were as follows: LDH, 4100 U/L; uric acid, 16 mg/dL; renal and liver tests were normal. There were 70% blasts on peripheral blood smear. Bone marrow examination showed 90% blasts. Flow cytometry showed an 86% blast rate; CD19, CD20, CD22, and TdT positivity, sIgM and CD34 negativity. The leukocyte count increased to 230,000/mm^3 on the second day of first relapse. The patient received 2 cycles of R-ICE (rituximab, ifosfamide, carboplatin, etoposide) chemotherapy protocol with no response. Thereafter the patient received a combination chemotherapy consisting of clofarabine, mitoxantrone, and rituximab, but no remission was achieved. The patient expired 4 months after the recurrence of the disease.

DISCUSSION

BL can exhibit with different immunophenotypically and morphologic features. In this report, our patient had an immature B-cell immunophenotype, atypical morphology, and cytogenetics, and FISH analysis revealed concurrent t(8;14) t(14;18) positivity. In the literature, a study reported that BL patients with precursor B-cell ALL immunophenotype, account for 0.1% of all ALL cases.[1] In this study, 5 BL patients without surface immunoglobulins exhibited L3 morphology and were t(8;14) positive. Precursor B-cell ALL treatment was initiated in these patients based on immunophenotyping, but then was switched to BL treatment following confirmation of translocation positivity. Complete remission was achieved in 4 of these 5 patients, who remained disease free during follow-up; the fifth patient relapsed 3 weeks after remission was achieved, but did not respond to reinduction treatment and died in 4 weeks. Although the study population was small, the prognosis of the disease was similar to that of classic BL. Hassan et al[3] administered BL treatment to a 4-year-old patient that presented with the precursor B-cell ALL immunophenotype, FAB L3 morphology, and with concurrent t(8;14); a clinical response similar to that of classical BL was achieved. Komrokji et al[4] reported an adult BL patient with the precursor B-cell ALL immunophenotype and atypical morphology, in which precursor B-cell ALL treatment was switched to BL treatment following detection of t(8;14). A case was reported by Sato et al[5] had the precursor B-cell ALL immunophenotype, L3 morphology, and with concurrent t(8;14). This patient also had chromosome 1q tetrasomy, which is considered to be associated with a poor prognosis. In this context, our case's immunophenotypical and morphologic findings were compatible with precursor B-cell ALL, but t(8;14) confirmed BL diagnosis. Taken together, these cases illustrate that sometimes immunophenotype is not compatible with a definitive diagnosis. As in our patient, also BL patients with the precursor B-cell ALL immunophenotype and L1-L2 morphology have been reported.[2,4,5] Conversely, there are few reports of immunophenotypically mature B-cell ALL (based on surface immunoglobulins, and CD19, CD20, and CD22); in which t(8;14), t(2;8), and t(8;22) are negative.[6–8] These patients were mostly treated according to a precursor B-cell ALL protocol and their prognosis was similar to that of seen in precursor B-cell ALL patients. In this regard, the presence of *MYC* rearrangement seems to be critically important to differentiate BL and precursor B-cell ALL, that can facilitate to differentiate and manage these rare patients.[9,10]

The translocation t(14;18), which leads to excessive secretion of antiapoptotic gene *Bcl-2*, is the most commonly observed translocation in B-cell malignancies. It is seen in 80% to 90% of all adult follicular lymphoma patients and in 30% of all adults patients with diffuse B-cell lymphoma.[11,12] *Bcl-2* is considered to be primarily inhibiting programmed cell death, but does not cause cells to acquire malignant properties. Activation of other oncogenes concomitantly or inactivation of tumor suppressor genes leads to tumor development.[12] There have been rare cases of de novo acute leukemia with concurrent t(14;18) reported. The association of *Bcl-2* and *MYC* rearrangement was first reported in 1983 by Mufti et al,[2] and the relationship between that association and poor prognosis was reported by Kramer et al.[13] The common features of these cases were high leukocyte counts and LDH levels that accompany advanced-stage disease, an aggressive course, and poor prognosis. Such patients may present with variable morphologic and phenotypical characteristics.[14–17] Atypical morphologic features and aggressive behavior are possibly due to overproduction of *Bcl-2* and *MYC*. A retrospective study that included 1350 lymphoma and leukemia (154 with B-cell ALL) patients reported that 24 of the patients had standard or variant *MYC* and *Bcl-2* positivity.[18] Analysis of previous acute leukemia cases involving *Bcl-2* and *MYC* gene translocations showed that most of the patients were adults and that only 2 of them were children (both 15 years old).[2,12–17,19,20] Our patient similarly exhibited both *Bcl-2* and *MYC* genes. Clinical findings of 3 pediatric patients with concurrent t(14;18) and *8q24/c-MYC* rearrangement are shown in Table 1.

In conclusion, in rare cases BL lymphoblasts exhibit the precursor B-cell ALL immunophenotype. According to the literature, such cases may be treated successfully using BL protocols and the prognosis is similar to that of classical BL. In contrast, it is known that patients with concurrent t(8;14) and t(14;18) can exhibit different immunophenotypical and morphologic features, and they have a poor prognosis, as in our patient. It is important to differentiate this rare entity by using immunophenotype,

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cytogenetic, pathologic, and immunohistochemistry analysis. To the best of our knowledge, it is the third pediatric ALL patient with concurrent t(8;14) and t(14;18) in the literature.

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