LETTER TO THE EDITOR

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Refractory Burkitt Lymphoma Following Acute Lymphoblastic Leukemia in a Patient with Homozygous *PMS2* Deficiency

Homozigot *PMS2* Eksikliği Olan Bir Hastada Akut Lenfoblastik Lösemi Sonrası Gelişen Refrakter Burkitt Lenfoma

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To the Editor,

Secondary malignancies develop in 1%-10% of children treated for acute lymphoblastic leukemia (ALL), with a relatively low risk of non-Hodgkin lymphoma in long-term survivors [1]. Constitutional mismatch repair deficiency (CMMRD) is known to increase the risk of hematological cancers [2], where timely diagnosis is crucial for incorporating novel therapeutics like immunotherapy as well as implementing cancer screening programs. [3]. Here, we report a patient with refractory Burkitt lymphoma following ALL with a delayed diagnosis of *PMS2* deficiency.

A $3^{9/12}$-year-old girl born from the marriage of first-degree cousins was diagnosed with high-risk pro-B-cell ALL. Three years after she completed chemotherapy, she developed abdominal Burkitt lymphoma. The 38-year-old father was in remission from colon cancer identified between his daughter's two diagnoses. Secondary cancer in the patient, paternal colon cancer, and a history of consanguineous marriage indicated the possibility of CMMRD [4]. However, whole-exome analysis (WES) yielded no evidence of a pathogenic variant. The patient responded partially after the third cycle and the last (sixth) cycle. The resected residual mass contained a viable tumor and a rapid local relapse was detected while preparing for high-dose therapy with autologous stem cell transplantation (HD-ASCT). Sequential treatments with rituximab + ifosfamide/carboplatin/etoposide (ICE), rituximab + CC, and ibrutinib + rituximab + ICE achieved only stable disease as the best response. A wide local excision was conducted, followed by HD-ASCT. Unfortunately, the patient died 3 months after the transplant due to recurrent progressive disease.

Given the strong indicators for CMMRD, the WES results were reassessed with an alternative bioinformatics program, which revealed a homozygous c.353+IG>T splice region variant in the *PMS2* gene. This variant is classified as "likely pathogenic" according to the criteria of the American College of Medical Genetics and Genomics (PMID: 25741868). Currently, there is no ClinVar or Human Gene Mutation Database registration for this variant. It is not found in healthy population databases (gnomAD) as heterozygous or homozygous. This variant is predicted to have a loss of function due to its location. We subsequently performed immunohistochemical analysis for mismatch repair proteins, revealing a loss of PMS2 expression.

Conventional chemotherapeutics induce cytotoxicity by DNA damage and rely on a functional mechanism to detect DNA replication errors and trigger apoptosis. Thus, CMMRD-associated tumors may show resistance and reduced responsiveness to standard chemotherapy regimens [5]. The aggressive behavior of these tumors is also enhanced by their hypermutant state [6], which presents a therapeutic opportunity as well. Immune checkpoint inhibitors have improved survival in CMMRD patients with mutational burden-high solid tumors [3,5,7]. Therefore, the accurate diagnosis of CMMRD is not only essential for the surveillance of the patient and the family members but also for the timely adoption of innovative therapeutics [8].

Genetic analyses are on their way to becoming standard tools in cancer management [9,10]. However, the rapidly evolving technologies impart new challenges, such as accurate analysis and interpretation [11]. In bioinformatics analysis programs, it is vital to determine the filters to be applied to define the variants to be analyzed. In addition, variants with low read depth should not be excluded, despite the analytical difficulties. If variants with low read depth have potential significance, they must be confirmed by additional molecular methods. When CMMRD is suspected in resource-limited settings, the

immunohistochemical expression of MLH1, MSH2, MSH6, and PMS2 proteins should first be analyzed as it is cheaper, faster, accessible, and easier to perform, followed by molecular testing if possible [8].

In conclusion, a history of consanguineous marriage along with secondary malignancies and Lynch syndrome spectrum tumors should remind of CMMRD. In the genomic era, clinicians should remain vigilant about potential false-negative results and collaborate with geneticists upon encountering discrepancies.

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Anahtar Sözcükler: Lösemi, Lenfoma, DNA yanlış eşleşme tamiri, Egzom analizi

Ethics

Informed Consent: The patient's parents provided informed consent for the case report.

Authorship Contributions

Surgical and Medical Practices: D.B.G., Z.Y.Y., M.E., Ö.T.; Concept: D.B.G., Z.Y.Y.; Design: D.B.G., Z.Y.Y., M.E.; Data Collection or Processing: D.B.G., A.A., Ö.T.; Analysis or Interpretation: D.B.G., A.A., Ö.T.; Literature Search: D.B.G., A.A.; Writing: D.B.G., M.E., A.A.

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