LETTERS TO THE EDITOR

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REFRACTORY BURKITT LYMPHOMA FOLLOWING ACUTE LYMPHOBLASTIC LEUKEMIA IN A PATIENT WITH HOMOZYGOUS PMS2 DEFICIENCY

Genç D.B. et al: Lymphoma following leukemia due to PMS2 deficiency

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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 well-known to increase the risk of hematological cancers[2], in which timely diagnosis is crucial for incorporating novel therapeutics like immunotherapy[3]. Herein, 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 a first-degree cousin marriage was diagnosed with high-risk proB-cell ALL. Three years after finishing her 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 a CMMRD[4]. However, the whole exome analysis (WES) yielded no evidence of a pathogenic variant. The patient responded partially after the third and the last (6^{th}) cycles. 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 only achieved stable disease as the best response. A wide local

excision followed by HD-ASCT, was conducted. Unfortunately, the patient died three months after the transplant due to recurrent progressive disease.

Given the strong indicators for CMMRD, 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 detected is classified as "likely pathogenic" according to ACMG criteria (PMID: 25741868). Currently, there is no ClinVar and HGMD registration regarding the 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 immunohistochemistry for MMR 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. 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, these rapidly evolving technologies convey new challenges such as accurate analysis and interpretation [11]. In bioinformatics analysis programs, it is vital to determine the filters applied to define the variants to be analyzed. In addition, variants with low-reading 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 the CMMRD is suspected in the resource-limited setting, immunohistochemical expression of MLH1, MSH2, MSH6, and PMS2 proteins should first be analyzed as it is cheaper, faster, accessible, and easy to perform, followed by molecular testing if available [8].

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

Keywords: Leukemia, lymphoma, DNA mismatch repair, exome analysis

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AUTHOR CONTRIBUTOR’S STATEMENT:
Dildar Bahar Genc gathered the data and designed and wrote the manuscript.
Zeynep Yıldız Yıldırmak contributed to the design of the manuscript, the acquisition of data, and the drafting.

Murat Elli contributed to the acquisition of data, and to the design and the review of the manuscript.
Akif Ayaz contributed to the conception, and the acquisition of data, and helped with the drafting and revision of the intellectual content.
Ozlem Ton contributed to the design of the manuscript, the acquisition of data, and the interpretation of the findings.
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