LETTER TO THE EDITOR

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A Sole p.G391E Mutation in *PML::RARA* Identified in Relapsed Acute Promyelocytic Leukemia

Nüks Akut Promiyelositik Lösemide *PML::RARA*'da Tanımlanan Tek p.G392E Mutasyonu

Zhan Su*, Tingxuan Wang*, Wei Yu, Xiaolin Ma, Huishou Fan, Xiangcong Yin, Wei Wang

The Affiliated Hospital of Qingdao University, Department of Hematology, Qingdao, China

To the Editor,

The *PML::RARA* fusion gene is the pathogenic driver of classic acute promyelocytic leukemia (APL) [1]. Mutations in *PML::RARA* occur in some patients, which may lead to resistance to all-trans retinoic acid (ATRA) or arsenic trioxide (ATO) [2]. Here, we describe a sole p.G391E mutation in the RARA moiety of *PML::RARA.*

In February 2023, a 36-year-old male patient was admitted to our hospital, presenting with ecchymosis and thrombocytopenia. A routine blood test showed white blood cell count of $2.17x10^9$/L, neutrophil count of $1.16x10^9$/L, hemoglobin of 138 g/L, and platelet count of $27x10^9$/L. A bone marrow smear showed 83.5% abnormal promyelocytes (Figure 1a). The typical t(15;17)(q24; q21) chromosomal translocation was observed (Figure 1b) and the *PML::RARA* fusion gene was positive. The diagnosis of low-risk APL was definitive. He received induction therapy with ATRA, ATO, and idarubicin. After attaining complete remission (CR), the patient received alternating oral therapy comprising ATRA and compound realgar natural indigo tablets.

In November 2023, the patient stopped taking his medication for several days. He developed thrombocytopenia and an increase in promyelocytes (23%) and *PML::RARA* (18.73%) in bone marrow (Figure 1c). Reinduction therapy was initiated with ATRA and ATO. After 10 days, there was no notable increase in blood leukocytes. Idarubicin (20 mg/day for 3 days) was then administered. Subsequent Sanger sequencing of *PML::RARA* pinpointed a p.G391E mutation within the ligand-binding domain (LBD) region of the RARA moiety (Figure 1d); hence, ATRA was temporarily halted. Following 18 days of induction therapy, a peripheral blood smear displayed 23% myelocytes and no promyelocytes. The leukemic cells were considered differentiated and ATRA was recommenced. It took a total of 1 month for the patient to achieve CR once again. Fortunately, the mutation was undetectable by real-time polymerase chain reaction, although there were minimal *PML::RARA* transcripts remaining.

Resistance to ATRA and ATO is partially attributed to mutations in the LBD of RARA and the PML-β2 domain, respectively [3,4]. To our knowledge, we are reporting a sole p.G391E mutation within *PML::RARA* for the first time. Notably, the mutation was heterozygous, indicating that mutation had occurred in a portion of blasts. The G391E mutation in *PML::RARA* was first reported by Goto et al. [5]. However, their patient also presented with an A216V mutation in the *PML* domain. Following a 10-month retinoic acid regimen, the patient developed resistance and ATRA was switched to ATO. The patient achieved a 7-year remission, but the efficacy of ATO gradually diminished [5]. It is noteworthy that *RARA* mutations frequently occur before *PML* mutations [6]. Furthermore, patients with only *RARA* mutations rather than *PML* mutations may achieve a second remission when treated with arsenic and ATRA [6]. However, the possibility of the mutated LBD partially retaining its affinity to ATRA cannot be ruled out. On the 18^{th} day of reinduction therapy, promyelocytes disappeared in the peripheral blood of our patient, suggesting that at least some promyelocytes might have undergone partial differentiation.

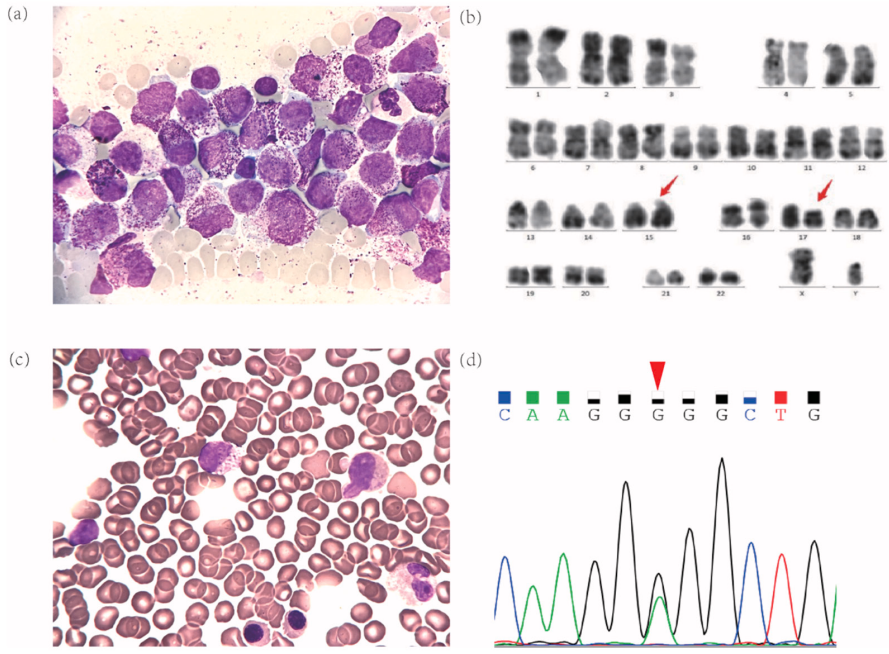

Figure 1. Bone marrow smear showed 83.5% abnormal promyelocytes (a); typical t(15;17)(q24; q21) chromosomal translocation was observed (b); after the patient stopped taking his medication, an increase in promyelocytes (23%) and *PML::RARA* (18.73%) in bone marrow occurred (c); Sanger sequencing of *PML::RARA* pinpointed a p.G391E (c.1172G>A) mutation within the ligand-binding domain region of the RARA moiety (d).

Keywords: Mutation, Relapse, Acute promyelocytic leukemia, *PML::RARA*

Anahtar Sözcükler: Mutasyon, Nüks, Akut promiyelositik lösemi, *PML::RARA*

Ethics

Informed Consent: Was received before submission of the manuscript.

Authorship Contributions

Surgical and Medical Practices: Z.S., W.W., W.Y., X.M., X.Y., H.F.; Concept: Z.S., W.W.; Design: Z.S., W.W.; Data Collection or Processing: T.W., H.F.; Analysis or Interpretation: Z.S.; X.Y.; Literature Search: Z.S., T.W.; Writing: Z.S., T.W.

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Address for Correspondence/Yazışma Adresi: Wei Wang, M.D., The Affiliated Hospital of Qingdao University, Department of Hematology, Qingdao, China
Phone : +86 0532 82911393
E-mail : 18661807392@163.com ORCID: orcid.org/0000-0003-3660-9945
***These authors contributed equally to this work.**

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