LETTERS TO THE EDITOR
DOI: 10.4274/tjh.galenos.2024.2024.0157

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

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April 30, 2024
July 8, 2024

To the Editor:

The *PML::RARA* fusion gene is the pathogenic driver of classic acute promyelocytic leukemia (APL). [1] Mutations in *PML::RARA* occurred in a proportion of patients, which may lead to resistance to ATRA or 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 was admitted to our hospital, presenting with ecchymosis and thrombocytopenia. The routine blood test showed a white blood cell（WBC） count of 2.17×109/L, neutrophil count of 1.16×109/L, hemoglobin 138g/L, and platelet 27×109/L. Bone marrow smear showed 83.5% abnormal promyelocytes(Figure 1a). Typical t(15;17)(q24; q21) chromosomal translocation (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 Tablet.

In November 2023, the patient took a break from 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 ten days, there was no notable increase in blood leukocytes. Then a prescription of idarubicin (20 mg/d for three days) was administered. Subsequent Sanger sequencing of *PML::RARA* pinpointed a p.G391E mutation within the LBD (ligand-binding domain) region of the RARA moiety (Figure 1d), and hence ATRA was

temporarily halted. Following a period of 18 days on induction therapy, a peripheral blood smear displayed 23% myelocytes and no promyelocytes. So, the leukemic cells were considered differentiated, and ATRA was recommenced. It took him a total of 1 month to achieve CR once again. Fortunately, the mutation was undetectable by RT-PCR, although there were minimal *PML::RARA* transcripts left.

The 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 best knowledge, we report the sole p.G391E mutation within *PML::RARA* for the first time. Notably, the mutation was heterozygous, indicating that the mutation occurred in a portion of blasts. The G391E mutation in *PML::RARA* was first reported by Emi et al. [5]. However, that patient 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 subsequently. The patient achieved a 7-year remission， whereas the efficacy of As2O3 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] That can't rule out the possibility that the mutated LBD might partially retain its affinity to ATRA. On the 18th day of reinduction therapy, promyelocytes disappeared in the peripheral blood of our patient, suggesting that at least some promyelocytes might have undergone partial differentiation.

Keywords
mutation; relapse; acute promyelocytic leukemia; *PML::RARA*

Statements and Declarations
There are no conflicts of interest to declare.

Ethics Informed Consent
Was received before submission.

Financial Disclosure
The authors declared that this study received no financial support.

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