To the Editor,

Acute promyelocytic leukemia (APL) is typified by the t (15;17) translocation that leads to the formation of the PML/RARA fusion gene and predicts a beneficial
response to retinoids[1]. However, approximately 10% of APL cases lack the classic t (15;17), detection of these variants APL is time consume and could be retinoid-resistant[1,2]. Therefore, early discriminate these variants of APL is extremely important, while could be invalid for the retinoid treatment and need other chemotherapy regimen[1]. Herein, we describe a case of ZBTB16-RARA APL, characterized by distinctive round promyelocyte cells with round nuclei in the peripheral blood or bone marrow, which could be an early diagnostic clue of this rare variant APL.

A 52-year-old male was admitted to our hospital with a 2-months history of fatigue with intermittment back pain. The results of other physical examinations were unremarkable. Initial hematological data showed a total leukocyte count of 24.7×10^9/L (3.5-9.5×10^9/L), neutrophil count of 13.4×10^9/L (1.8-6.3×10^9/L), hemoglobin concentration of 123g/L, platelet count of 203×10^9/L (85-303×10^9/L) and 7.4% distinctive promyelocyte cell in the peripheral blood. Interestingly, 15% of promyelocytes were round, also with round nuclei (Figure 1A, black arrow). Coagulation function indicated fibrinogen 4.1g/L (1.8-3.5g/L), and D-dimer 11.9mg/L (0-0.55 mg/L). Further biochemical screening did not show significant change. Thus, the above results indicated the APL and bone marrow aspiration was performed. Further bone marrow aspiration illustrated hypercellularity, with a myeloid-to-erythroid ratio of 12:1, and 47% of dystrophic promyelocytes. They were irregular, hypergranular, non-lobed or round nuclei with immature chromatin and nucleolus, occasionally intracytoplasmic Auer rods. Strikingly, 25% of dystrophic promyelocytes were round promyelocyte cells with round nuclei (Figure 1B, black arrow). A myeloperoxidase reaction was strongly positive for these APL cells. Immunophenotyping indicated a profile of promyelocytic cells (CD117, CD33, cMPO, CD56, CD9) without other aberrant marker expression. In addition, the erythroid was repressed to 5%, and only six megakaryocytes were noted throughout the smear, indicating that the erythroid and megakaryocytic lineages were affected. Thus, the APL was diagnosed on this patient. However, the conventional PML/RARA fusion gene was not detected in this patient, which was inconsistent with APL diagnosis. Then the blood sample was sent to the next generation sequence examinations, and results revealed the ZBTB16-RARA fusion gene. One month later, the cytogenetic result was t (11;17)(q23;q21), which confirm the APL diagnosis in this patient. This variant ZBTB16-RARA translocation is reported in less than 1% of APL patients and is associated with a distinctly worse prognosis than t (15; 17) APL, as patients fail to respond to the maturation effect of all-trans-retinoic acid[2,3]. Thus, this case highlights the atypical morphological features of promyelocytes[2,3] (particularly a distinctive round promyelocyte cell with round nuclei morphological notation), which is critical for the diagnosis of this rare ZBTB16-RARA APL.

Author contribution: Yang Su and Xiaoming Fan provided the picture, clinical data
and guided the clinical diagnosis. Jiwei Zhao and Wei Yang participate the data analysis and writing. Jinlin Liu designed the study and wrote the manuscript.

**Ethical Approval:** This study has been approved by the ethical committee of Sichuan Provincial People's Hospital, China.

**References**

**Figure 1.** Peripheral blood and bone marrow smears taken from a ZBTB16-RARA acute promyelocytic leukemia patient. (A,B) Large distinctive round promyelocyte cells with round nuclei were observed in the peripheral blood (A) or bone marrow (B) (magnification, 1000×, Wright-Giemsa staining)