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# Round Promyelocyte Cells with Round Nuclei: Clues to the Diagnosis of *ZBTB16-RARA* Acute Promyelocytic Leukemia

## Yuvarlak Çekirdekçikli Yuvarlak Promyelosit Hücreler: *ZBTB16-RARA* Akut Promyelositik Lösemi Tanısı için İpuçları

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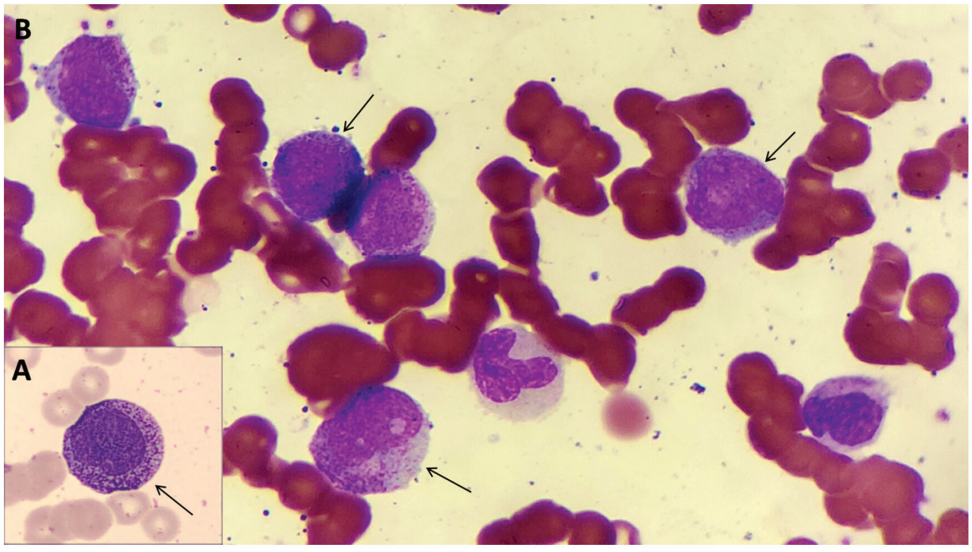


**Figure 1.** Peripheral blood and bone marrow smears taken from a patient with *ZBTB16-RARA* acute promyelocytic leukemia. Large distinctive round promyelocyte cells with round nuclei were observed in the peripheral blood **(A)** and bone marrow **(B)** (magnification: 1000$^{x}$, Wright-Giemsa staining).

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), and detection of these variants of APL, which could be retinoid-resistant, is time-consuming [1,2]. Therefore, early discrimination of these variants of APL is extremely important, making it possible to identify patients who will not respond to retinoid treatment and will need other che motherapy regimens [1]. Herein, we describe a case of *ZBTB16-RARA* APL characterized by distinctive round promyelocyte cells with round nuclei in the peripheral blood and bone marrow, which could be an early diagnostic clue to this rare variant of APL.

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A 52-year-old male was admitted to our hospital with a 2-month history of fatigue with intermittent back pain. The results of other physical examinations were unremarkable. Initial hematological data revealed a total leukocyte count of 24.7x$10^9$/L (normal range: 3.5-9.5x$10^9$/L), neutrophil count of 13.4x$10^9$/L (normal range: 1.8-6.3x$10^9$/L), hemoglobin of 123 g/L, platelet count of 203x$10^9$/L (normal range: 85-303x$10^9$/L), and 7.4% distinctive promyelocyte cells in the peripheral blood. Interestingly, 15% of the promyelocytes were rounded and also had round nuclei (Figure 1A, black arrow). Coagulation testing indicated fibrinogen of 4.1 g/L (normal range: 1.8-3.5 g/L) and D-dimer of 11.9 mg/L (normal range: 0-0.55 mg/L). Further biochemical screening did not show significant changes. Thus, the above results indicated APL and bone marrow aspiration was performed.

Further bone marrow aspiration illustrated hypercellularity, with a myeloid-to-erythroid ratio of 12:1 and 47% dystrophic promyelocytes. They were irregular and hypergranular, with non-lobed or round nuclei and immature chromatin and nucleoli, occasionally with intracytoplasmic Auer rods. Strikingly, 25% of the dystrophic promyelocytes were round promyelocyte cells with round nuclei (Figure 1B, black arrow). Myeloperoxidase staining was strongly positive for these APL cells. Immunophenotyping indicated a profile of promyelocytic cells (CD117, CD33, cMPO, CD56, and CD9) without other aberrant marker expression. In addition, erythroid cells were repressed to 5% and only six megakaryocytes were noted throughout the smear, indicating that the erythroid and megakaryocytic lineages were affected. Thus, the patient was diagnosed with APL. However, the conventional *PML/RARA* fusion gene was not detected in this case, which was inconsistent with the APL diagnosis. A blood sample was then sent for next-generation sequencing examinations and the results revealed the *ZBTB16-RARA* fusion gene. One month later, the cytogenetic result was t(11;17)(q23;q21), which confirmed the patient's APL diagnosis.

This variant *ZBTB16-RARA* translocation is reported in less than 1% of APL cases and is associated with a distinctly worse prognosis than t(15; 17) APL, as these 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], and particularly the distinctive morphology of round promyelocyte cells with round nuclei, which is critical for the diagnosis of this rare APL variant.

**Keywords:** Round promyelocyte cell, Round nuclei, *ZBTB16-RARA*, Acute promyelocytic leukemia

**Anahtar Sözcükler:** Yuvarlak promyelosit hücreler, Yuvarlak çekirdekçik, *ZBTB16-RARA*, Akut promyelositik lösemi

### Ethics

**Informed Consent:** Written consent was obtained for the patient in this case.

### Authorship Contributions

Concept: L.J.; Design: L.J.; Data Collection or Processing: Y.S., J.Z., X.F.; Analysis or Interpretation: Y.S., J.Z., X.F.; Literature Search: W.Y., J.L.; Writing: W.Y., J.L.

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