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BRIEF COMMUNICATION

Strange Bedfellows: *NPM1* Mutations in Acute Promyelocytic Leukemia

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To the Editor: In a recent article in *Hematology/Oncology and Stem Cell Therapy*, Nath et al. [1] address the incidence of common genetic alterations in a cohort of patients with *PML-RARA*-positive acute promyelocytic leukemia (APL) and report co-existing *NPM1* mutations in 38% (11/29) of patients. Despite this "striking observation," the authors do not relate this finding to complete remission rate and overall survival, and consider this phenomenon only briefly in discussion. The presence of *NPM1* mutations in APL patients and in such a high number merits further consideration.

According to the World Health Organization classification of myeloid neoplasms and acute leukemia, APL with *PML-RARA* and acute myeloid leukemia (AML) with mutated *NPM1* are considered distinct clinicopathological entities. Each rearrangement contributes to leukemogenesis by divergent mechanisms: in APL, PML-RARA exerts dominant-negative effects on RAR/RXR-dependent transcriptional control through the recruitment of co-repressor complexes with the direct or indirect regulation of target genes responsible for the differentiation block, aberrant self-renewal, and impairment of autophagy and apoptosis [2], whereas in AML, mutant NPM1 contributes to genomic instability, loss of tumor suppressor function, inhibition of apoptosis, increased MYC protein, and interference of HOX gene expression [3]. Given initial studies of *NPM1* mutations found them mutually exclusive from other types of AML with recurrent genetic abnormalities [4] and with subsequent sequencing of large, international APL cohorts identifying mutations of *FLT3*, *WT1*, and *NRAS* as the most frequently co-existing mutations [5,6], the findings of Nath et al. [1] either represent an exceptional geographical variation in APL genotype or raise the possibility of a methodological discrepancy.

The authors cite a previous study from India in which *NPM1* mutations were detected in 45% (18/40) of patients characterized as APL, though this study does not explicitly state whether all APL patients had evidence of the t(15;17) or a *PML-RARA* fusion [7]. A further report from India provides an incidence of *NPM1* mutations in cytogenetically confirmed APL as 7% (2/28 patients) [8], and together these findings might suggest a true genotypic variant in Indian patients with APL. Confirmation of the *PML-RARA* fusion should always be sought and annotated in such studies as *NPM1*-positive AML can immunophenotypically and morphologically mimic APL [9]. *NPM1* mutations can be detected by numerous technologies including capillary electrophoresis and real-time PCR with next-generation sequencing increasingly adopted, while Nath et al. [1] screen for *NPM1* mutations by an unconventional Sanger sequencing approach. Given the "striking observation" reported and its possible implications for molecular classification, measurable residual disease monitoring, and targeted therapy, *NPM1* mutations in APL patients should ideally be confirmed or refuted by an alternative methodology as advocated [10].

Declaration of Competing Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Nath S, Bhattacharyya J, Chandra P, Saxena R, Sazawal S, Saikia KK. Clinicopathological significance of common

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genetic alterations in patients with acute promyelocytic leukemia. Hematol Oncol Stem Cell Ther 2020. https://doi.org/10.1016/j.hemonc.2020.07.004.
[2] Noguera NI, Catalano G, Banella C, Divona M, Faraoni I, Ottone T, et al. Acute promyelocytic leukemia: update on the mechanisms of leukemogenesis, resistance and on innovative treatment strategies. Cancers 2019;11:1591. https://doi.org/10.3390/cancers1110591.
[3] Zarka J, Short NJ, Kanagal-Shamanna, Issa GC. Nucleophosmin1 mutations in acute myeloid leukemia. Genes 2020; 11:649. https://doi.org/10.3390/genes11060649.
[4] Falini B, Mecucci C, Saglio G, Lo Coco F, Diverio D, Brown P, et al. NPM1 mutations and cytoplasmic nucleophosmin are mutually exclusive of recurrent genetic abnormalities: a comparative analysis of 2562 patients with acute myeloid leukemia. Haematologica 2008;93:439–42. https://doi.org/10.3324/haematol.12153.
[5] Madan V, Shyamsunder P, Han L, Mayakonda A, Nagata Y, Sundaresan J, et al. Comprehensive mutational analysis of primary and relapse acute promyelocytic leukemia. Leukemia 2016;20:1672–81. https://doi.org/10.1038/leu.2016.237.
[6] Iaccarino L, Ottone T, Alfonso V, Cicconi L, Divona M, Lavorgna S, et al. Mutational landscape of patients with acute promyelocytic leukemia at diagnosis and relapse. Am J Hematol 2019;94:1091–7. https://doi.org/10.1002/ajh.25573.
[7] Swaminathan S, Garg S, Madkaikar M, Gupta M, Jijina F, Ghosh K. FLT3 and NPM-1 mutations in a cohort of acute promyelocytic leukemia patients from India. Indian J Hum Genet 2014;20:160–5. https://doi.org/10.4103/0971-6866.142884.
[8] Ahmad F, Mandava S, Das BR. Mutations of NPM1 gene in de novo acute myeloid leukaemia: determination of incidence, distribution pattern and identification of two novel mutations in Indian population. Hematol Oncol 2009;27: 90–7. https://doi.org/10.1002/hon.883.
[9] Oelschlaegel U, Mohr B, Schaich M, Schäkel U, Kroschinsky F, Illmer T, et al. HLA-DRneg patients without acute promyelocytic leukemia show distinct immunophenotypic, genetic, molecular, and cytomorphological characteristics compared to acute promyelocytic leukemia. Cytometry B Clin Cytom 2009;76:321–7. https://doi.org/10.1002/cyto.b.20475.
[10] Kumar D, Mehta A, Panigrahi MK, Nath S, Saikia KK. NPM1 mutation analysis in acute myeloid leukemia: comparison of three techniques – Sanger sequencing, pyrosequencing, and real-time polymerase chain reaction. Turk J Haematol 2018; 35:49–53. https://doi.org/10.4274/tjh.2017.0095.