haematologica
Journal of the Ferrata Storti Foundation

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*by Giovanni Barosi, Vittorio Rosti, Luca Malcovati and Robert Peter Gale*

*Received: May 11, 2026.*
*Accepted: May 13, 2026.*

*Citation: Giovanni Barosi, Vittorio Rosti, Luca Malcovati and Robert Peter Gale. Response to Comment on: “Clonal megakaryocyte dysplasia with normal blood values: a covert, thrombosis-prone, early myeloproliferative neoplasm”.*
*Haematologica. 2026 May 21. doi: 10.3324/haematol.2026.301242 [Epub ahead of print]*

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Response to Comment on: “Clonal megakaryocyte dysplasia with normal blood values: a covert, thrombosis-prone, early myeloproliferative neoplasm.”

Giovanni Barosi,[1] Vittorio Rosti,[1] Luca Malcovati,[2] Robert Peter Gale.[3]

1. Center for the Study of Myelofibrosis, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Pavia, Italy.
2. Division of Molecular Hematology and Precision Medicine, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo and University of Pavia, Pavia, Italy.
3. Centre for Haematology, Department of Immunology and Inflammation, Imperial College of Science, Technology and Medicine, London, UK.

Correspondence: Giovanni Barosi MD. Center for the Study of Myelofibrosis. IRCCS Policlinico S. Matteo. Viale Golgi 19. 27100 Pavia, Italy. E-mail: g.barosi@smatteo.pv.it

Authors Contributions: The authors contributed equally to the letter.

Disclosures. Robert Peter Gale is a consultant to BeiGene Ltd., Fusion Pharma LLC, LaJolla NanoMedical Inc., Mingsight Parmaceuticals Inc., Kite Pharma and CStone Pharmaceuticals; Advisor to Antegene Biotech LLC, Medical Director and FFF Enterprises Inc.; Partner in AZACA Inc.; Board of Directors, RakFond Foundation for Cancer Research Support; Scientific Advisory Board, StemRad Ltd.

We thank Prof. Lichtman for his thoughtful, encouraging comments regarding our proposal to delineate a distinct variant within the spectrum of myeloproliferative neoplasms (MPNs), which we have termed *clonal megakaryocyte dysplasia with normal blood values* (CMD-NBV).[1] As we stated in the manuscript, our primary objective was to persuade the scientific community of the conceptual and clinical value of recognizing this phenotype as a separate entity within the already complex MPN landscape.

Prof. Lichtman's principal concern relates to the simultaneous use of the terms *hyperplastic*, *dysplastic*, and *neoplastic* in describing megakaryocytes in this entity. This apparent overlap is clarified by distinguishing the semantic domains to which each term belongs. The term *clonal* - and by extension *neoplastic* - is used in our definition to denote the biological nature of the variant, which, as part of the MPN category, inherently carries the designation of a neoplasm. We note many clonal entities like warts, atherosclerotic plaques, clonal hematopoiesis of indeterminate potential (CHIP) and paroxysmal nocturnal hemoglobinuria (PNH) are clonal but not neoplastic. In contrast, *dysplastic* refers strictly to the histological appearance of megakaryocytes. We acknowledge that we have used the term in a narrower sense compared with the definition in general pathology, where dysplasia denotes abnormal or disordered cellular development often regarded as precancerous. We also acknowledge that "dysplasia" is traditionally associated with myelodysplastic syndromes (MDS) when applied to megakaryocyte histology. However, in contemporary hematopathology, the term more broadly describes histological abnormalities across a range of hematologic conditions, malignant and non-malignant. Of relevance is the report of Chisholm *et al.* who described *isolated megakaryocytic dysplasia* in people with a germline *RUNX1* variant causing familial platelet disorder with associated myeloid malignancy. [2] Atypical megakaryocytes, predominantly small forms with hypolobated or eccentric nuclei and increased nuclear-to-cytoplasmic ratios, reflect the underlying germline *RUNX1* variant and were not diagnostic of MDS. Notably, one of the 30 patients in our series of CMD-NBV cases carried a germline *RUNX1* variant, supporting the appropriateness of the term in selected contexts.[3]

Finally, the term *hyperplasia* refers to a quantitative expansion of the megakaryocytic lineage in the bone marrow, consistent with its standard definition as an increase in tissue mass resulting from cellular proliferation.

Prof. Lichtman proposes an alternative designation, "clonal megakaryocytic dysmorphia." We appreciate this constructive suggestion and view it as a valuable

contribution to what we envision will become a consensus-building process by which a panel of expert hematologists will refine and agree upon a nomenclature which best captures the biological, histological, and clinical features of this emerging MPN variant.

References

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