haematologica
Journal of the Ferrata Storti Foundation

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Received: April 28, 2026.
Accepted: May 6, 2026.

Citation: Marshall A. Lichtman. Hyperplasia, dysplasia and neoplasia are unique pathological entities. Comment on: "Clonal megakaryocyte dysplasia with normal blood values: a covert, thrombosis-prone, early myeloproliferative neoplasm".
Haematologica. 2026 May 14. doi: 10.3324/haematol.2026.301164 [Epub ahead of print]

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Hyperplasia, dysplasia and neoplasia are unique pathological entities. Comment on: "Clonal megakaryocyte dysplasia with normal blood values: a covert, thrombosis-prone, early myeloproliferative neoplasm"

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Disclosures: none

I write to comment on the interesting and comprehensive report of 30 patients with an indolent myeloid neoplasm, with a prominent accumulation of neoplastic megakaryocytes in the marrow and, often, with normal blood cell counts, which was published in *Haematologia* by Professor Barosi and colleagues.[1] This rare, but interesting, syndrome is consequential notably for a high frequency of arterial or venous thrombotic disease. The authors designated it "clonal megakaryocyte dysplasia" with normal blood values: a covert, thrombosis-prone, early myeloproliferative neoplasm.

I was struck by the designation "clonal dysplasia" and that the marrow megakaryocytic expansion was described as "megakaryocytic hyperplasia". That is, in this report the cells were described as hyperplastic, dysplastic and neoplastic, simultaneously. Should one be concerned about the identification and designation of distinct pathological entities that represent either an (i) aplasia or hypoplasia, (ii) hyperplasia, (iii) metaplasia, (iv) dysplasia or (v) neoplasia? Are we at the point that these specific, classical pathological entities, of which neoplasia is uniquely monoclonal and associated with oncogenic gene mutations, can be used interchangeably? Is specificity of pathological designations no longer relevant or meaningful.[2-4] The woman with uterine cervical dysplasia is relieved; but, the woman with uterine cervical neoplasia is not. The almost universal dysmorphia of neoplasia is not dysplasia. The unfortunate decision to designate it so was made at a symposium at L' Institute de Pathologie Cellulaire in Kremlin Bicétre, France, the proceedings of which were published in 1976.[5] An uninformed decision was made to designated these neoplasms, overt leukemic transformations, "hematopoietic dysplasias" (later, shortened to myelodysplasia). They were overtly neoplastic (not dysplastic) diseases. The striking and characteristic dysmorphia of blood and marrow cells in these neoplasms distracted these otherwise astute observers.[5,6] This aberrant consensus has led to a half-century of word

salad. Thus, these neoplasms went uncatalogued in the United States for over 70 years (circa 1930's to 2001) before the U.S. National Cancer Institute, SEER program, appreciated that they were neoplasms.[7]

The authors of the paper under discussion designate this syndrome as a specific disease, entitled "clonal megakaryocytic dysplasia with normal blood values (CMD-NBV)". The newly identified manifestation of the clonal expansion of a neoplastic hematopoietic multipotential progenitor cell disease is worthy of a specific designation. I, however, encourage the naming authority to avoid designating it simultaneously as a neoplasia and a dysplasia, a logical impossibility. "Clonal" is sufficient to the task as in "clonal megakaryocytic disease". Clonal megakaryocytic disease is described as "early" but "indolent" may be preferable (at least from a proliferative standpoint). Since it is usually associated with normal blood counts, it may be present for some time before a thrombosis leads to its discovery.

The World Health Organization committees that set the nomenclature used in the classification of myeloid neoplasms have embraced an oxymoron "neoplastic dysplasia". A simple change from dysplasia to dysmorphia would solve this etymological problem. Dysmorphia speaks to altered morphology, usually as a result of a germline gene mutation. Although it has not been used for somatic mutations, ordinarily, there is no reason not to do so. Thus, if this new syndrome is characterized by clonal megakaryocytic dysmorphia that would avoid this biological impossibility, capture the intent of the authors and preserve the classical distinction between dysplasia and neoplasia and set a very useful precedent.

Having had my say on nomenclature, my congratulations to Professor Barosi and colleagues on the clinical description and extensive evaluation of the gene mutations associated with this uncommon and indolent pathobiological form of myeloid neoplasm. It is a very unusual

example of the ability of a transformed (neoplastic) multipotential hematopoietic progenitor cell to be dressed in many disguises. This variation is a compelling aspect of neoplasia of a cell in this primitive hematopoietic compartment. The opportunities of (i) variation in its differentiation into the progenitors of any, some or all of at least nine lineages, (ii) the subsequent variable maturation of each lineage into any of several levels of precursors and (iii) the variable further maturation to phenocopies of mature blood cells are large, making the potential phenotypes innumerable, although most can be clustered into a specific designation.[8,9] They are each, however, neoplasms (clonal with evident or occasionally occult gene mutations with our current techniques).

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