Is it primary myelofibrosis or chronic megakaryocytic leukemia?

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In 1879, Heuck is credited with describing a disorder under the title "Two Cases of Leukemia and Peculiar Blood and Bone Marrow Findings",[1] which is considered the first description of what is today designated *primary myelofibrosis* by the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues.[2] Since the description by Heuck 143 years ago, numerous designations for the disease have been proposed or used, and different ones have been preferred in different countries. The designations: (i) agnogenic myeloid metaplasia,[a] (ii) myelofibrosis with myeloid metaplasia, (iii) primary myelofibrosis–osteosclerosis, and (iv) idiopathic (primary) myelofibrosis are among the over 30 designations given to the disease.[3] Remarkably, the first three designations cited above were used in the title of three papers on the topic by the same senior author.[4] The current "official' designation of *primary myelofibrosis* is a profound pathobiological misnomer.

No concise designation can been formulated that accommodates the constellation of 11 characteristic phenotypic features of this clonal (neoplastic) hematopoietic multipotential cell abnormality, which Heuck called "peculiar": (i) anemia, (ii) dacryocytes in the blood, (iii) myelocytes in the blood, (iv) variable alterations (increases or decreases) in the steady-state level of neutrophils and platelets (usually elevation), (v) orthochromatic erythroblasts in the blood, (vi) increased $CD34^+$ cells in the blood, (vii) dominant neoplastic megakaryocytopoiesis, (viii) a reactive marrow fibrosis, (ix) a propensity to extramedullary fibrohematopoietic tumors, (x) a risk of developing osteosclerosis and (xi) splenomegaly, sometimes massive. Its genetic profile consists of mutations of *JAK2* (60%), *CALR* (25%), or *MPL* (5%) in 90% of cases. In so-called triple-negative disease, other mutations characteristic of hematopoietic neoplasms may be found.[2,5] The nosological dilemma is not a surprise since no practical designation could accommodate the varied manifestations of several neoplastic myeloid diseases.[6] Which fundamental abnormality should be given primacy? Not fibrosis, an epiphenomenon and a connective tissue fiber.

The constant, indeed central pathophysiological feature, of so-called primary myelofibrosis is the expansion of neoplastic, profoundly dysmorphic[b] megakaryocytes in the marrow. It, thus, could (should) be designated chronic megakaryocytic leukemia, adhering to the principle that myelogenous leukemias have multiple phenotypes, reflecting the differentiation options of both the normal and mutated multipotential hematopoietic progenitor cell, the presumptive site of the foundational mutations of this family of neoplasms. The resultant neoplastic phenotypes are usually designated by the lineage that either dominates the marrow (e.g., acute promyelocytic leukemia) or is the most important pathobiological feature (e.g., chronic neutrophilic leukemia). The designation may be supplemented by its principal genetic mutations, if relatively prevalent, for example, acute myelogenous leukemia, t(8;21)(q22;q22).

In primary myelofibrosis, the megakaryocytic alterations are the most prevalent, the most constant and the most important diagnostically and pathogenically. Neoplastic expansion of megakaryocytopoiesis, megakaryocyte clusters, often around marrow sinuses, loss of anchoring to the abluminal aspect of the marrow sinus with entry of whole megakaryocytes into the sinus lumen, pleomorphic changes of megakaryocytic nuclei, sometimes described as cloud-like, as a result of nuclear ballooning and abnormal variability of nuclear and cytoplasmic features are striking. Dysmorphic platelets, megakaryocyte cytoplasmic fragments and bare megakaryocyte nuclei in the blood may be seen, especially in advanced cases. Following splenectomy, the blood contains a remarkable array of bizarre and giant platelets, megakaryocyte cytoplasmic fragments and dysmorphic micromegakaryocytes. The dominance of neoplastic megakaryocytopoiesis is evident also in cases with intense marrow fibrosis and reductions in erythropoiesis and granulopoiesis. In this setting, the bundles of reticulin (type III collagen) and other types of collagen abut arrays of dysmorphic megakaryocytes. Abnormal megakaryocytopoiesis, also, is the hallmark of patients in the prefibrotic phase of the disease.

In striking support of these phenotypic findings, blood CD34 cells isolated from patients with primary myelofibrosis resulted in 24-fold and 800-fold greater numbers of $CD41^+$ cells (putative megakaryocytes) than the $CD34^+$ cells obtained from healthy volunteers administered granulocyte colony-stimulating factor or the $CD34^+$ cells isolated from patients with polycythemia vera, respectively.[7] Megakaryocytes from patients with primary myelofibrosis had delayed apoptosis and overexpressed the anti-apoptotic protein BCL-xL. Media conditioned with CD61 cells (a megakaryocyte marker) from patients with primary myelofibrosis contained higher levels of transforming

growth factor-β and active matrix metalloproteinase-9 than media from normal individuals or from patients with polycythemia vera.[7] These findings were true if the mutation in the cells of patients with primary myelofibrosis was *JAK2* or not. Neoplastic megakaryocytopoiesis is the dominant feature of incipient, prototypic or advanced myelofibrosis and supports the designation of chronic megakaryocytic leukemia.

One could ask whether essential (primary) thrombocythemia is not, also, a chronic megakaryocytic leukemia? It is one in the sense that it is a clonal disorder originating in a primitive multipotential hematopoietic cell in which its principal expression is exaggerated neoplastic megakaryocytopoiesis and elevated platelet counts, but the term thrombocythemia captures the central issue. It is, in effect, an indolent myelogenous leukemia if one uses the term "myelogenous leukemia" to designate the spectrum of neoplasms that originate in a mutated multipotential hematopoietic progenitor cell, as we do for the overwhelming majority of those disorders. Moreover, primary thrombocythemia is never associated with leukemic blast cells in blood or marrow. Indolent myelogenous leukemia is a counterpoint to acute (polyblastic) and subacute (oligoblastic) myelogenous leukemias and is not meant to imply the absence of morbidity. It, too, carries a risk of clonal evolution to a more severe myeloid neoplasm, notably acute myelogenous leukemia. I do not suggest changing its name, as the term "leukemia" has come to mean something to the laity with which the patient with thrombocythemia should not be confronted, as is the case with polycythemia vera, another neoplasm of the multipotential progenitor cell (an indolent myelogenous leukemia with a risk of evolution to acute myelogenous leukemia). In the case of polycythemia, indolent leukemia is characterized by differentiation of the mutant hematopoietic multipotential cell, such that it provides clonal platelets, neutrophils, other granulocytes and red cells that are phenocopies of normal cells and highly functional. The distinction of thrombocythemia from chronic megakaryocytic leukemia (primary myelofibrosis in the WHO classification) is a profound one, as noted by the markedly longer life expectancy on average of a patient with thrombocythemia (median survival of 20 years) at the time of diagnosis as compared to a patient with primary myelofibrosis who has a median survival of 5 years after diagnosis.[5] Thus, the nosological grouping (chronic myeloproliferative neoplasms) of polycythemia vera, thrombocythemia and so-called primary myelofibrosis has a genetic basis but primary myelofibrosis (chronic megakaryocytic leukemia) has a strikingly different course, management and prognosis. In 1942, amidst the Nazi occupation of France, and at a time in which there was a primitive understanding of multipotential hematopoietic progenitor cell neoplasms, Chevallier discussed the "odoleukemias".[8] He chose the Greek word, *odo*, meaning threshold, to highlight disorders that are on the threshold of overt leukemia. Chevallier proposed "leucoses" as the generic term for "leucémie" so that marked variations in white cell and blast counts and other presenting features would not engender inappropriate terminology.

Of the numerous prior designations for primary myelofibrosis, "megakaryocytic myelosis" may have been the most apt. It highlighted the primary phenomenon. Indeed, the choice of primary myelofibrosis by the WHO panel was contentious because of the frequency of a prefibrotic phase of the disease, making "primary myelofibrosis without fibrosis" a state that Aristotle would find irreconcilable with his dictum that a proposition cannot be both true and false simultaneously (The Principle of Non-Contradiction). Some preferred the term chronic megakaryocytic–granulocytic myelosis, but that group did not win the day, despite this designation being more accurate. If they had substituted "leukemia" for "myelosis" (a neologism) and dropped the term granulocytic, they would have hit the bulls-eye. Neoplastic granulocytic expansion with neutrophilia is a frequent early event in this disease, but like most other chronic clonal myeloid disorders, this reflects its origin in a primitive hematopoietic multipotential progenitor cell; the major myeloid lineages are involved in one way or another in all clonal myeloid diseases. The term 'myelosis', although euphonious is a euphemism for myelogenous leukemia. There does not seem to be a hesitation to call the disease acute megakaryocytic leukemia when neoplastic megakaryocytes dominate in that setting. The two most inappropriate features of the WHO designation, "primary myelofibrosis" are that: (i) the fibrosis is secondary, an epiphenomenon of the neoplastic megakaryocytes exaggerated cytokine release and their stimulation of marrow fibroblasts (reticular cells) to synthesize various types of collagen, but notably type III (reticular fibers);[c] and (ii) it is inappropriate to name a neoplasm after a connective tissue fiber as opposed to a relevant neoplastic cell. The naming decision reflects the failure to give priority to the essential feature and instead to an epiphenomenon and a feature that does not highlight the neoplastic cells central to the malignancy.

The designation chronic megakaryocytic leukemia: (i) reflects the principal and most constant neoplastic alteration in the disease, (ii) corresponds to the nomenclature for other clonal myeloid diseases and neoplasms in general, (iii) assists in decreasing (all too gradually) anachronistic and erroneous terminology, (iv) implies multilineage hematopoietic involvement (myelogenous leukemia), (v) implies the epiphenomena of marrow fibrosis, osteosclerosis, and fibrohematopoietic extramedullary tumors, and (vi) indicates the propensity, through clonal evolution, to terminate in an acute myelogenous leukemia.

Disclosures

No conflicts of interest to disclose.

Footnotes:

[a]The term "metaplasia" was applied inaccurately to this neoplasm over 80 years ago.[9] Metaplasia is the transformation of one differentiated cell type to another differentiated cell type, usually evident in epithelia. Technically there is no evidence of metaplasia in the tissues of patients with primary myelofibrosis. That appellation would require cells intrinsic to spleen, liver or lymph nodes changing to a different histology resulting in the spleen, liver or lymph nodes converting to hematopoietic marrow. In addition, metaplasia is not neoplasia. The evidence for effective hematopoiesis in the spleen, its most likely site, is largely dispelled by the improvement in or absence of an effect on blood cell counts after removal of massively enlarged spleens.[10] The marked increase in circulating $CD34^+$ cells may seed the spleen, liver or lymph nodes but there is no evidence that they establish effective hematopoiesis. Moreover, the phenomenon of increased circulating $CD34^+$ cells is closer to metastasis than metaplasia, the precise definition of which is not met by any of the changes observed in primary myelofibrosis.

[b]I use the term dysmorphia, not dysplasia, because neoplastic cells cannot be dysplastic.[11] Neoplasia and dysplasia are two *qualitatively* (uniquely) different pathological states. Aplasia or hypoplasia, hyperplasia, metaplasia, dysplasia, and neoplasia are distinct pathological processes. Only one, neoplasia, is monoclonal; the others are each polyclonal, a fundamental distinction. The Oxford Languages defines dysmorphia in two distinct ways. One designates dysmorphia as a deformity or abnormality in the shape or size of a specific body part that may have a genetic basis, which in the case of myeloid neoplasms is usually an acquired somatic mutation(s).

[c]The fibroplasia in marrow is complex and 11 connective tissue proteins may be elevated in the marrow in primary myelofibrosis as well as several cytokines that provoke collagen formation. Collagen types I, II, IV, and V may be elevated in marrow, but type III collagen (reticulin) is increased uniformly and preferentially. Increased peptides of procollagen and other connective tissue proteins (e.g., laminin and fibronectin) are increased in plasma. See Prchal *et al.*[5] for comprehensive details of these epiphenomenologic changes.

References

1. Heuck G. Zwei Fälle von Leukämie mit eigenthümlichem Blut- resp Knochenmarksbefund. [Two cases of leukemia with peculiar blood and bone marrow findings]. Virchows Arch (Pathol Anat). 1879;78:475.
2. Swedlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue. International Agency for Research on Cancer. 2017:44-49.
3. Pettigrew JD, Ward HP. Correlation of radiologic, histologic, and clinical findings in agnogenic myeloid metaplasia. Radiology. 1969:93:541-548.
4. Lichtman MA. Is it chronic idiopathic myelofibrosis, myelofibrosis with myeloid metaplasia, chronic megakaryocytic-granulocytic myelosis, or chronic megakaryocytic leukemia? Further thoughts on the nosology of the clonal myeloid disorders. Leukemia. 2005;19(7):1139-1141.
5. Prchal JT, Lichtman MA. Primary myelofibrosis, Chap. 85. In: Kaushansky K, Lichtman MA, Prchal JT, Levi M, Burns LJ, Linch DC, eds. Williams Hematology. 10th ed. New York: McGraw Hill Education. 2021:1389-1410.
6. Lichtman MA, Classification and clinical manifestations of the clonal myeloid diseases, Chap. 82. In: Kaushansky K, Lichtman MA, Prchal JT, Levi M, Burns LJ, Linch DC, eds. Williams Hematology. 10th ed. New York: McGraw Hill Education, 2021:1343-1359.
7. Ciurea, SO, Merchant, D, Mahmud N, et al. Pivotal contributions of megakaryocytes to the biology of idiopathic myelofibrosis. Blood. 2007;110(3):986-993.
8. Chevalier, P. Sur la terminologie des leucoses et les affections-frontières les odoleucoses. Sang. 1943;15:587-594.
9. Jackson H Jr, Parker F, Lemon HM. Agnogenic myeloid metaplasia of the spleen - a syndrome simulating other more definite hematologic disorders. N Engl J Med. 1940;222:985-994.
10. Green TW, Conley CL, Ashburn LL, Peters HR. Splenectomy for myeloid metaplasia of the spleen. N Engl J Med. 1953;248(6):211.
11. Lichtman MA. Myelodysplasia or myeloneoplasia: thoughts on the nosology of clonal myeloid diseases. Blood Cells Mol Dis. 2000;26(6):572-581.