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Received: February 10, 2022.
Accepted: March 8, 2022.

Citation: Marshall A. Lichtman. Is it primary myelofibrosis or chronic megakaryocytic leukemia?

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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 Classification of Tumours of Haematopoietic and Lymphoid Tissues.² Since the description by Heuck 143 years ago, numerous designations for the disease had been proposed or used, and different ones have been preferred in different countries. The designations (i) agnogenic myeloid metaplasia³, (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 be formulated that accommodates the constellation of eleven characteristic phenotypic features of this clonal (neoplastic) hematopoietic multipotential cell abnormality that 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.⁵,² 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 pathophysiologica feature, of so-called primary myelofibrosis is the expansion of neoplastic, profoundly dysmorphic⁵ megakaryocytes in the marrow. It, thus, could (should) be designated chronic megakaryocytic leukemia, adhering to the principal 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 [e.g. 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 pathogenetically. Neoplastic expansion of megakaryocytopenosis, 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 balloononing 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 megakaryocytopenosis 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 megakaryocytopenosis, 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. 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. These finding were true if the mutation in the cells of patients with primary myelofibrosis was JAK2 or not. Neoplastic megakaryocytopenosis is the dominant feature of incipient, prototypical 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 clonal disorder originating in a primitive multipotential hematopoietic cell in which its principal expression is exaggerated neoplastic megakaryocytopenosis 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 not meant to imply the absence of morbidity. It, also, 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 thrombocytemia 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 thrombocytemia 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 thrombocytemia (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. Thus, the nosological grouping (chronic myeloproliferative neoplasms) of polycythemia vera, thrombocytemia 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 “odo-leukemias”. 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 it being a more accurate designation. 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); 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 (a) reflects the principal and most constant neoplastic alteration in the disease, (b) corresponds to the nomenclature for other clonal myeloid diseases and neoplasms in general, (c) assists in decreasing (all too gradually) anachronistic and erroneous terminology, (d) implies multilineage hematopoietic involvement (myelogenous leukemia), (e) implies the epiphenomena of marrow fibrosis, osteosclerosis, and fibrohematopoietic extramedullary tumors, and (f) indicates the propensity, through clonal evolution, to terminate in an acute myelogenous leukemia.

Footnotes:

† The term “metaplasia” was applied inaccurately to this neoplasm over 80 years ago. 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. The marked increase in circulating CD34+ cells may seed the spleen, liver or lymph nodes but there is no evidence they establish effective hematopoiesis. Moreover, the increased circulating CD34+ cells phenomenon is closer to metastasis than metaplasia, which precise definition is not met by any of the changes observed in primary myelofibrosis.

§ I use the term dysmorphia, not dysplasia, because neoplastic cells cannot be dysplastic. Neoplasia and dysplasia are two qualitatively (uniquely) different pathologic 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 the deformity or abnormality in the shape or size of a specific body part that may have a genetic basis, which in the case myeloid neoplasms is usually an acquired somatic mutation(s).

* The fibroplasia in marrow is complex and eleven 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, 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, fibronectin) are increased in plasma. See reference 5 for comprehensive details of these epiphenomenologic changes.
References


