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Classical BCR: *ABL1*-Negative Myeloproliferative Neoplasms: News in the Diagnosis from the 2022 International Consensus Classification of Hematological Malignancies

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Given their clinical, laboratory, and evolving features, and their distinction from *BCR:: ABL1*-positive chronic myeloid leukemia (Philadelphia chromosome [t(9;22)(q34;q11) translocation]-positive chronic myeloid leukemia in the past), Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (PMF) are included together in a group of diseases known as 'classical *BCR::ABL1*-negative myeloproliferative neoplasms' (**Table 1**) [1].

Table 1: Myeloproliferative neoplasms according to the 2022 International Consensus Classification of hematological malignancies [1].

Chronic Myeloid Leukemia (CML)
Polycythemia Vera (PV)
Essential Thrombocythemia (ET)
Primary Myelofibrosis (PMF)
Early/Prefibrotic Primary Myelofibrosis (pre-PMF)
Overt Primary Myelofibrosis (overt PMF)
Chronic Neutrophilic Leukemia (CNL)
Chronic Eosinophilic Leukemia, Not Otherwise Specified (CEL, NOS)
Myeloproliferative Neoplasm, Unclassifiable (MPN-U)

Particular of Table 1 in Arber et al. [1].

Here we report the diagnostic criteria for these diseases according to the 2022 International Consensus Classification (ICC) of Myeloid and Lymphoid Neoplasms [1-3], a major revision of the previous editions of the World Health Organization (WHO) publications on the same topic [4-12]. Although the ICC is not affiliated with the WHO, the 2022 ICC happened with the contribution of many authors of the prior WHO classifications. We agree that the cornerstone of the diagnosis of the classical *BCR:: ABL1*-negative myeloproliferative neoplasms, like that of other hematological malignancies, is represented by the integration of molecular findings with bone marrow morphology and blood counts [1]. For this reason, the accurate identification of myeloproliferative neoplasm-associated driver mutations, *JAK2* V617F, *JAK2* exon 12, *MPL* W515L/K, and Calreticulin (*CALR*) by highly sensitive single target approaches (quantitative reverse transcriptase polymerase chain reaction, digital droplet polymerase chain reaction) or multitarget panel/next-generation sequencing assays with a minimal sensitivity of variant allele frequency (VAF 1%) detection, is important to support the diagnosis of these diseases and to separate wild-type or triple-negative cases. In triple-negative cases, a search for non-canonical *JAK2* and *MPL* mutations (the latter for suspected ET and PMF) is encouraged,

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whereas a *JAK2* V617F VAF of <1% should prompt the search for coexisting canonical *CALR* (and *MPL*) mutations [1]. Before touching on the diagnostic criteria identified by the ICC for the three single myeloproliferative neoplasms considered here, we also anticipate that the grading of bone marrow fibrosis, which may be present in the three diseases, remains unchanged with respect to the 2016 WHO classification (**Table 2**) [1,11].

Table 2: Myeloproliferative neoplasms according to the 2022 International Consensus Classification of hematological malignancies [1].

MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal bone marrow
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis*
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis*

Semiquantitative grading of bone Marrow Fibrosis (MF) with minor modifications concerning collagen and osteosclerosis. Fiber density should be assessed only in hematopoietic areas.

* In grades MF-2 or MF-3 an additional trichrome stain is recommended.

Partially modified from Arber et al. [11].

Primary myelofibrosis

Compared with the criteria for the diagnosis of PMF in the 2016 revision of the WHO classification [11], those in the new ICC are not particularly different (**Table 3**) [1]. The subdivision of the disease into two phases, i.e., the early pre-fibrotic stage (pre-PMF) and the overt fibrotic stage (overt PMF), is confirmed. This subdivision had already been described in the 2016 WHO revision [11] but not in the 2008 WHO classification [8]. The only difference between the 2022 ICC and the 2016 WHO revision is that, according to the ICC, the diagnostic criteria (all 3 major criteria and at least 1 minor criterion) for pre-PMF or overt PMF must be confirmed at two consecutive determinations [1], a clarification that was not made in the 2016 WHO classification [11].

Table 3: Diagnostic criteria for primary myelofibrosis according to the 2022 International Consensus Classification of hematological neoplasms [1].

PMF, early/prefibrotic stage (pre-PMF)	PMF, overt fibrotic stage
Major criteria 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* bone marrow fibrosis grade <2, increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased erythropoiesis 2. *JAK2, CALR*, or *MPL* mutation† or presence of another clonal marker‡ or absence of reactive bone marrow reticulin fibrosis§ 3. Diagnostic criteria for *BCR::ABL1*-positive CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms are not met Minor criteria • Anemia not attributed to a comorbid condition • Leukocytosis ≥ 11 x 10^9/L • Palpable splenomegaly • Lactate dehydrogenase level above the reference range	Major criteria 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* accompanied by reticulin and/or collagen fibrosis grades 2 or 3 2. *JAK2, CALR*, or *MPL* mutation† or presence of another clonal marker‡ or absence of reactive myelofibrosis§ 3. Diagnostic criteria for ET, PV, *BCR-ABL1*-positive CML, myelodysplastic syndrome, or other myeloid neoplasms‖ are not met Minor criteria: • Anemia not attributed to a comorbid condition • Leukocytosis ≥ 11 x 10^9/ L • Palpable splenomegaly • Lactate dehydrogenase level above the reference range • Leukoerythroblastosis
The diagnosis of pre-PMF or overt PMF requires all 3 major criteria and at least 1 minor criterion confirmed in two consecutive determinations	

PMF: Primary Myelofibrosis; CML: Chronic Myeloid Leukemia; PV: Polycythemia Vera; ET: Essential Thrombocytopenia.

* On morphological examination, megakaryocytes in pre-PMF and overt PMF usually demonstrates a higher degree of megakaryocytic atypia than in any other subtype of myeloproliferative neoplasms; distinctive features of megakaryocytes include small to giant megakaryocytes with a prevalence of severe maturation defects (cloud-like, hypolobulated, and hyperchromatic nuclei) and presence of abnormal large dense clusters (mostly >6 megakaryocytes lying strictly adjacent).

† It is recommended that highly sensitive assays are used for *JAK2* V617F (sensitivity level < 1%) and *CALR* and *MPL* (sensitivity level 1% to 3%); in negative cases, consider searching for noncanonical *JAK2* and *MPL* mutations.

‡ Assessed by cytogenetics or sensitive next-generation techniques; detection of mutations associated with myeloid neoplasms (e.g., *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SF3B1*, *SRSF2* and *TET2* mutations) supports the clonal nature of the disease.

§ Minimal reticulin fibrosis (grade 1) secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or another lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

‖ Monocytosis can be present at diagnosis or develop during the course of PMF; in these cases, a history of MPN excludes Chronic Myelomonocytic Leukemia (CMML), whereas a higher variant allelic frequency for MPN-associated driver mutations supports the diagnosis of PMF with monocytosis rather than CMML.

Partially modified from Arber et al. [1].

Essential thrombocythemia

For a better distinction of ET from PMF, the 2022 ICC, unlike the 2016 WHO classification [11], emphasizes the subdivision of ET into two disease phases, that of an initial pre-fibrotic stage, properly named ET, and that of a more advanced fibrotic stage named post-ET myelofibrosis (post-ET MF) (**Table 4**) [1].

Table 4: Diagnostic criteria for Essential Thrombocythemia (ET) and post-ET myelofibrosis according to the 2022 International Consensus Classification of hematological neoplasms [1].

Essential thrombocythemia	Post-essential thrombocytopenia myelofibrosis
Major criteria 1. Platelet count ≥450 x 10^9/L 2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters;* no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant bone marrow fibrosis† 3. Diagnostic criteria for *BCR::ABL1*-positive CML, PV, PMF, or other myeloid neoplasms are not met 4. *JAK2, CALR*, or *MPL* mutation‡ Minor criterion • Presence of a clonal marker§ or absence of evidence of reactive thrombocytosis‖	Major criteria 1. Previous established diagnosis of ET 2. Bone marrow fibrosis of grade 2 or 3 Additional criteria 1. Anemia (i.e., below the reference range given age, sex, and altitude considerations) and a >2 g/dL decrease from baseline hemoglobin concentration 2. Leukoerythroblastosis 3. Increase in palpable splenomegaly of > 5 cm from baseline or the development of a newly palpable splenomegaly 4. Elevated LDH level above the reference range 5. Development of any 2 (or all 3) of the following constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)
The diagnosis of ET requires either all major criteria or the first 3 major criteria plus the minor criterion	The diagnosis of post-ET MF is established by all required criteria and at least 2 additional criteria

ET: Essential Thrombocythemia; CML: Chronic Myeloid Leukemia; PV: Polycythemia Vera; PMF: Primary Myelofibrosis; LDH: Lactate Dehydrogenase; MF: Myelofibrosis.

* Three or more megakaryocytes lying adjacent without other bone marrow cells in between; in most of these rare clusters ≤6 megakaryocytes may be observed, increase in huge clusters (>6 cells) accompanied by granulocytic proliferation is a morphological hallmark of pre-PMF (Table 3).

† Very rarely a minor increase in reticulin fibers (grade 1) may occur at initial diagnosis.

‡ It is recommended that highly sensitive assays are used for *JAK2* V617F (sensitivity level < 1%) and *CALR* and *MPL* (sensitivity level 1% to 3%); in negative cases, consider a search for noncanonical *JAK2* and *MPL* mutations.

§ Assessed by cytogenetics or sensitive next-generation sequencing techniques.

‖ Reactive causes of thrombocytosis include a variety of underlying conditions such as iron deficiency, chronic infection, chronic inflammatory disease, medication, neoplasia, or history of splenectomy.

Partially modified from Arber et al. [1].

Table 5: Diagnostic criteria for Polycythemia Vera (PV) and post-PV myelofibrosis according to the 2022 International Consensus Classification of hematological neoplasms [1].

Polycythemia vera	Post-polycythemia vera myelofibrosis
Major criteria 1. Elevated hemoglobin concentration or elevated hematocrit or increased red blood cell mass* 2. Presence of *JAK2* V617F or *JAK2* exon 12 mutation† 3. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megacaryocytes without atypia Minor criteria • Subnormal serum erythropoietin level	Major criteria 1. Previous established diagnosis of PV 2. Bone marrow fibrosis of grade 2 or 3 Additional criteria 1. Anemia (i.e., below the reference range given age, sex, and altitude considerations) or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or or cytoreductive treatment for erythrocytosis 2. Leukoerythroblastosis 3. Increase in palpable splenomegaly of > 5 cm from baseline or the development of a newly palpable splenomegaly 4. Development of any 2 (or all 3) of the following constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (<37.5°C)
The diagnosis of PV requires either all 3 major criteria or the first 2 major criteria plus the minor criterion‡	The diagnosis of post-PV myelofibrosis is established by all required criteria and at least 2 additional criteria

* Diagnostic thresholds: hemoglobin: >16.5 g/dL in men and >16.0 g/dL in women; hematocrit: >49% in men and >48% in women; red blood cell mass: >25% above mean normal predicted value.

† It is recommended that highly sensitive assays are used for *JAK2* V617F (sensitivity level < 1%); in negative cases, consider searching for atypical *JAK2* mutations in exons 12 to 15.

‡ A bone marrow biopsy may not be required in patients with sustained absolute erythrocytosis (hemoglobin concentration of >18.5 g/dL in men or >16.5 g/dL in women and hematocrit values of >55.5% in men or >49.5% in women) and the presence of a *JAK2* V617F or *JAK2* exon 12 mutation.

Partially modified from Arber et al. [1].

It is important to note in this regard that dense clustering of megakaryocytes (3 or more megakaryocytes lying adjacent without other bone marrow cells in between), although generally accepted as the morphological hallmark of PMF, does not exclude the diagnosis of ET, because infrequently small megakaryocytic clusters may be present even in this subtype. However, compared to patients with pre-PMF, those with ET usually present with normal white blood cell counts, no anemia, normal lactate dehydrogenase values, less frequent splenomegaly and lower numbers of CD34-positive progenitor cells in peripheral blood and bone marrow. The distinction is important because ET has a lower risk of myelofibrotic progression (i.e., post-ET

MF), ranging between 0.8% and 4.5% at 10 years, and a very low risk of transformation, with the reported 10-year cumulative incidence of having more than 20% of peripheral blood/bone marrow blasts being between 0.7% and 1.9% [1].

Polycythemia vera

As for ET, for a better distinction of PV from PMF, the revised 2022 ICC, unlike the 2016 WHO classification [11], recognizes a more advanced and fibrotic stage of the disease, called post-PV Myelofibrosis (post-PV MF) (**Table 5**) [1].

In PV, a high VAF for *JAK2* V617F is associated with older age, higher hemoglobin level, leukocytosis, and lower platelet count. *JAK2* exon 12 mutated cases have a similar prognosis to that of JAK2 V61/F mutated cases, although they may occur at a younger age. Because a proportion of these cases may have isolated erythrocytosis associated with erythroid preponderance in the bone marrow, the diagnostic criterion of pan-myelosis may not be applicable to this subset of patients [1].

Considerations

As described above, we have reported here the 2022 ICC diagnostic criteria for the classical *BCR:: ABL1*-negative myeloproliferative neoplasms, a group of diseases notoriously constituted by PMF, ET, and PV [1]. As announced in the presentation of the new classification of these diseases, morphology continues to represent a fundamental element in the definition of hematological neoplasms, *BCR:: ABL1*-negative myeloproliferative neoplasms included. However, acknowledging that the abnormal morphology is a result of dysregulated hematopoiesis driven by somatic gene mutations or altered expression, the ICC considers genomic features more extensively. This is because defining nosological entities based on underlying molecular mechanism(s) of disease is fundamental for enabling the development of precision treatments [2].

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