Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel

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Perspectives

Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel

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The Janus kinase 2 mutation, *JAK2*617V>F, is myeloid neoplasm-specific; its presence excludes secondary polycythemia, thrombocytosis, or bone marrow fibrosis from other causes. Furthermore, *JAK2*617V>F or a *JAK2* exon 12 mutation is present in virtually all patients with polycythemia vera (PV), whereas *JAK2*617V>F also occurs in approximately half of patients with essential thrombocythemia (ET) or primary myelofibrosis (PMF). Therefore, *JAK2* mutation screening holds the promise of a decisive diagnostic test in PV while being complementary to histology for the diagnosis of ET and PMF; the combination of molecular testing and histologic review should also facilitate diagnosis of ET associated with borderline thrombocytosis. Accordingly, revision of the current World Health Organization (WHO) diagnostic criteria for PV, ET, and PMF is warranted; *JAK2* mutation analysis should be listed as a major criterion for PV diagnosis, and the platelet count threshold for ET diagnosis can be lowered from 600 to 450 × 10^9/L. The current document was prepared by an international expert panel of pathologists and clinical investigators in myeloproliferative disorders; it was subsequently presented to members of the Clinical Advisory Committee for the revision of the WHO Classification of Myeloid Neoplasms, who endorsed the document and recommended its adoption by the WHO. (Blood. 2007;110:1092-1097)

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Introduction

Recent discoveries in the molecular pathogenesis of *BCR-ABL*–negative myeloproliferative disorders (MPDs) have raised the prospect of genetic classification and molecular diagnosis in these disorders.[1] The seminal reports in this regard were first published in early 2005 and described a somatic Janus kinase 2 (*JAK2*) mutation (*JAK2*617V>F; an exon 14 somatic 1849G>T mutation) in polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF)[2-5]; mutational frequency is estimated at 95% for PV and 50% for both ET and PMF. Subsequently, *JAK2*617V>F was demonstrated in other myeloid neoplasms, albeit at a much lower mutational frequency.[6,7] Most recently, other MPD-associated *JAK2* (exon 12 mutations)[8] and *MPL* (*MPL*515W>L/K)[9] mutations were described, the former in *JAK2*617V>F-negative PV[8] and the latter in < 5% of patients with PMF or ET.[9,10] As such, a *JAK2* mutation is present in virtually all patients with PV and thus constitutes a sensitive diagnostic marker for the disease. In addition, the incidence of *JAK2*617V>F in both ET and PMF is high enough to warrant diagnostic utility that is complementary to histologic impression.

Prompted by these developments, members of the Steering Committee for the revision of the World Health Organization (WHO) Classification of Hematopoietic and Lymphoid Neoplasms approached key members of the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT), the Myeloproliferative Diseases-Research Consortium (MPD-RC), and the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) to enlist their cooperation in the development of revised diagnostic guidelines for the *BCR-ABL*-negative MPDs. E-conferences were initiated by 2 of the authors (A.T. and J.W.V.). The key participants are listed as coauthors of the current document and include clinical investigators, scientists, and pathologists, 2 of whom are members of the WHO Steering Committee (J.W.V. and J.T.). The resulting consensus document was also presented to members of the Clinical Advisory Committee for the revision of the WHO Classification of Myeloid Neoplasms (meeting March 10, 2007, Chicago IL, Clara D. Bloomfield, Chair), who endorsed the document and recommended its adoption by the WHO.

Rationale for revising WHO criteria for the diagnosis of polycythemia vera

Table 1 outlines the current WHO criteria for the diagnosis of PV. As mentioned above, virtually all patients with overt (elevated hematocrit) or inapparent (hematocrit that does not exceed the upper reference range) PV carry *JAK2*617V>F or another functionally similar *JAK2* mutation (exon 12 *JAK2* mutations). Such mutations are

Table 1. 2001 WHO criteria for polycythemia vera

2001 criteria for PV
A-criteria
1. Elevated red cell mass > 25% above mean normal predicted value, or hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women, or > 99th percentile of method-specific reference range for age, sex, altitude of residence
2. No cause of secondary erythrocytosis, including:
a. Absence of familial erythrocytosis
b. No elevation of erythropoietin caused by:
i. Hypoxia (arterial $pO_2 \leq 92\%$)
ii. High oxygen affinity hemoglobin
iii. Truncated erythropoietin receptor
iv. Inappropriate erythropoietin production by tumor
3. Splenomegaly
4. Clonal genetic abnormality other than Philadelphia chromosome or *BCR-ABL* fusion gene in marrow cells
5. Endogenous erythroid colony formation
B-criteria
1. Thrombocytosis > 400×10^9/L
2. Leukocytosis > 12×10^9/L
3. Bone marrow biopsy showing panmyelosis with prominent erythroid and megakaryocytic proliferation
4. Low serum erythropoietin levels

Diagnosis requires the presence of the first 2 A-criteria together with either any 1 other A-criterion or 2 B-criteria.

absent in either secondary or spurious polycythemia. Therefore, most of the current WHO criteria, listed under either A-criteria or B-criteria (Table 1) are no longer necessary and can be replaced by adding "presence of *JAK2*617V>F or other functionally similar *JAK2* mutation" as a major criterion (Table 2). Accordingly, we propose to replace the current list under the A-criteria with two "major" criteria: (1) laboratory evidence of increased hemoglobin, hematocrit, or red cell mass and (2) the presence of a *JAK2* mutation (Table 2). Similarly, we propose to replace the current list of B-criteria with 3 biologically relevant "minor" criteria: (1) MPD-consistent bone marrow histology, (2) serum erythropoietin level below the reference range for normal, and (3) presence of endogenous erythroid colonies. Diagnosis of PV under the new proposed criteria will require either the presence of both major criteria and at least one minor criterion or the presence of the first major criterion and at least two minor criteria (Table 2).

In practice, meeting both of the newly proposed major criteria should capture more than 97% of cases with PV. However, to minimize consequences of false-positive molecular test results and further optimize diagnostic specificity, the additional presence of at least one of the 3 minor criteria will be required to make a diagnosis of PV (Table 2). The alternative diagnostic combination (first major criterion plus 2 minor criteria) should capture occasional cases of true PV that might be either negative for a known *JAK2* mutation or associated with a mutation burden that is too low to be detected.[11] The requirement for two instead of one minor criteria in this instance reinforces the accuracy associated with each test and increases the comfort level to make the specific diagnosis in the context of a negative molecular test result.

The first major criterion, under the newly proposed criteria (Table 2), is notably different from that listed in the existing WHO criteria (Table 1). First, while retaining the hemoglobin and red cell mass threshold levels for PV diagnosis used in the current WHO criteria, the new first major criterion incorporates information on hematocrit to address potential discordance between hemoglobin level and hematocrit and accommodate the needs of medical centers that use hematocrit instead of hemoglobin level as their primary tool to evaluate polycythemia.[12] We are very much aware

of the controversies regarding which one of the 3 red cell parameters (hemoglobin level, hematocrit value, and measured red cell mass) is the most accurate in the determination of red cell volume. However, we do not believe that the issue will be resolved any time soon; thus, we opted to accommodate individual choice on the matter. The second modification of the first major criterion for PV diagnosis (Table 2) aspires to capture biologically true PV cases with a documented, sustained increase in their baseline hemoglobin level in excess of 20 g/L (2 g/dL), without reaching the diagnostic threshold. The particular measure helps bypass the need for red cell mass measurement in such cases and complements bone marrow histology in identifying early PV cases.

We recognize the possibility that the newly revised criteria could still miss occult PV. However, the identification of such cases might not be therapeutically relevant because (1) high-risk MPD patients receive similar drug therapy regardless of the specific MPD diagnosis and (2) the value of aggressive phlebotomy in aspirin-treated low-risk disease, within hematocrit ranges between 0.4 and 0.55 (40% and 55%), has been questioned by the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) investigators.[13] The newly proposed criteria will also allow identification of "atypical" or "early" PV that presents with the phenotype of "idiopathic erythrocytosis"[14] because such cases have now been identified to display either exon 14 or exon 12 *JAK2* mutations.[11,15] Some cases of idiopathic erythrocytosis remain molecularly undefined, but we do not believe that the situation warrants establishment of a separate set of diagnostic criteria. We are also aware of the possibility that certain cases of *JAK2* mutation-positive "idiopathic" abdominal vein thrombosis could progress into overt PV but more information is needed in this regard before recognizing such cases in formal diagnostic criteria.[16]

Finally, hemoglobin level is expected to be lower in the presence of iron deficiency, which confounds the accurate interpretation of the hemoglobin/hematocrit level. However, for the purposes of research or clinical trials, a formal PV diagnosis requires demonstration of meeting the WHO criteria in terms of hemoglobin/hematocrit level after iron replacement. Whether or not such a measure is clinically prudent is left to the discretion of the physician. In other words, in routine clinical practice, one should not be prevented from making a working diagnosis of PV, in the presence of iron deficiency, just because the WHO criteria are not met.

Table 2. Proposed revised WHO criteria for polycythemia vera

Proposed criteria for PV
Major criteria
1. Hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume*
2. Presence of *JAK2*617V>F or other functionally similar mutation such as *JAK2* exon 12 mutation
Minor criteria
1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
2. Serum erythropoietin level below the reference range for normal
3. Endogenous erythroid colony formation in vitro

Diagnosis requires the presence of both major criteria and 1 minor criterion or the presence of the first major criterion together with 2 minor criteria.

*Hemoglobin or hematocrit greater than 99th percentile of method-specific reference range for age, sex, altitude of residence or hemoglobin greater than 17 g/dL in men, 15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from an individual's baseline value that can not be attributed to correction of iron deficiency, or elevated red cell mass greater than 25% above mean normal predicted value.

Rationale for revising WHO criteria for the diagnosis of essential thrombocythemia

Table 3 outlines current WHO criteria for the diagnosis of ET. Many investigators have effectively argued that the use of 600×10^9/L platelets as a threshold level compromises the detection of early-phase disease because the 95th percentile for normal platelet count, adjusted for gender and race, is below 400×10^9/L.[17-21] Therefore, we start by proposing a change in the platelet threshold level required for ET diagnosis by lowering it to 450×10^9/L from 600×10^9/L (Table 4, criterion 1); a proposal supported by the current availability of a clonal marker (*JAK2*617V>F) that is present in 50% of ET patients. However, unlike the case with PV, the utility of mutation screening for *JAK2*617V>F for the diagnosis of ET or PMF is limited by suboptimal negative predictive value and lack of diagnostic specificity within the context of myeloid neoplasms.[7,22] Therefore, a bone marrow biopsy is still required to help with the differential diagnosis between *JAK2*617V>F-negative ET and reactive thrombocytosis and to differentiate ET from other chronic myeloid neoplasms, including cellular phase/prefibrotic PMF and myelodysplastic syndromes (MDS).[23] As such, we propose keeping bone marrow examination as one of the required criteria for ET diagnosis (Table 4, criterion 2).

In addition, we propose getting rid of separate categorization of negative exclusionary criteria and instead suggest the addition of two criteria (criteria 3 and 4), which serve in the same capacity, to the main list (Table 4). Criterion 3 requires the absence of WHO criteria that would otherwise classify a patient as having PV, PMF, chronic myelogenous leukemia (CML), or MDS. In this regard, it is important to exclude occult PV in the iron-deficient patient by a trial of iron replacement therapy. Similarly, careful bone marrow histologic assessment is necessary to exclude the possibility of cellular phase/prefibrotic PMF or MDS. Criterion 4 underlines the need to exclude reactive thrombocytosis either through the demonstration of *JAK2*617V>F or, in mutation-negative patients, by clinical assessment.[23,24] Accordingly, the diagnosis of ET would

Table 3. 2001 World Health Organization criteria for essential thrombocythemia

2001 criteria for ET
Positive criteria
1. Sustained platelet count $\geq 600 \times 10^9$/L
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes
Criteria of exclusion
1. No evidence of polycythemia vera
a. Normal red cell mass or hemoglobin < 18.5 g/dL in men, 16.5 g/dL in women
b. Stainable iron in marrow, normal serum ferritin, or normal MCV
c. If the former condition is not met, failure of iron trial to increase red cell mass or hemoglobin levels to the PV range
2. No evidence of chronic myeloid leukemia: no Philadelphia chromosome and no *BCR-ABL* fusion gene
3. No evidence of chronic idiopathic myelofibrosis
a. Collagen fibrosis absent
b. Reticulin fibrosis minimal or absent
4. No evidence of myelodysplastic syndrome
a. No del(5q), t(3;3)(q21;q26), inv(3)(q21q26)
b. No significant granulocytic dysplasia, few, if any, micromegakaryocytes
5. No evidence that thrombocytosis is reactive caused by
a. Underlying inflammation or infection
b. Underlying neoplasm
c. Prior splenectomy

Table 4. Proposed revised WHO criteria for essential thrombocythemia (ET)

Proposed criteria for ET
1. Sustained platelet count $\geq 450 \times 10^9$/L*
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes; no significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis
3. Not meeting WHO criteria for PV,† PMF,‡ CML,§ MDS,¶ or other myeloid neoplasm
4. Demonstration of *JAK2*617V>F or other clonal marker, or in the absence of a clonal marker, no evidence for reactive thrombocytosis‖

Diagnosis requires meeting all 4 criteria.

* During the work-up period.

† Requires the failure of iron replacement therapy to increase hemoglobin level to the PV range in the presence of decreased serum ferritin. Exclusion of PV is based on hemoglobin and hematocrit levels, and red cell mass measurement is not required.

‡ Requires the absence of relevant reticulin fibrosis, collagen fibrosis, peripheral blood leukoerythroblastosis, or markedly hypercellular marrow for age accompanied by megakaryocyte morphology that is typical for PMF− small to large with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous or irregularly folded nuclei and dense clustering.

§ Requires the absence of *BCR-ABL*.

¶ Requires absence of dyserythropoiesis and dysgranulopoiesis.

‖ Causes of reactive thrombocytosis include iron deficiency, splenectomy, surgery, infection, inflammation, connective tissue disease, metastatic cancer, and lymphoproliferative disorders. However, the presence of a condition associated with reactive thrombocytosis does not exclude the possibility of ET if the first three criteria are met.

require fulfillment of all 4 main criteria listed in Table 4. However, it is possible that a *JAK2*617V>F-negative ET patient might have a concomitant condition known to be associated with reactive thrombocytosis. In this instance, diagnosis of ET can be made provided the first 3 criteria are met.

In ET, bone marrow findings are remarkable for the presence of large, but mature-appearing, megakaryocytes with deeply lobulated and hyperlobulated nuclei that are most often dispersed throughout the biopsy sections, but sometimes also found in loose clusters.[25] Often the bone marrow is normally or only slightly hypercellular for the patient's age, and the increased trilineage proliferation (panmyelosis) that characterizes PV or the granulocytic proliferation and highly bizarre megakaryocytes that characterize the prefibrotic stage of PMF are not found in ET.[26] The presence of dyserythropoiesis, macrocytosis, monocytosis, pseudo Pelger-Huet anomaly, or other dysgranulopoietic changes of neutrophils and/or predominance of small megakaryocytes with monolobated nuclei suggest MDS rather than ET.[23,27] On the other hand, a spectrum of cytogenetic abnormalities, including del(20q), del(5q), and unbalanced whole-arm translocation between 1q and 7p have been reported in otherwise typical ET[28,29] and their presence, unless accompanied by histologic features of MDS, should not exclude the diagnosis of ET.[30] Nevertheless, we encourage obtaining cytogenetic studies at time of diagnostic bone marrow examination for ET and re-evaluation of the histologic impression in the case of unusual findings.

Rationale for revising WHO criteria for the diagnosis of PMF

The current WHO criteria for PMF[31] have separate tables for "prefibrotic" and "fibrotic" PMF (Tables 5,6). Under the newly proposed revised criteria (Table 7), 3 major and 4 minor criteria are enlisted. The first major criterion underscores histology as a critical diagnostic criterion for PMF. In this regard, there is little doubt about the existence of the histopathologic phenotype of PMF with

Table 5. 2001 WHO criteria for prefibrotic stage primary myelofibrosis

2001 criteria for prefibrotic PMF
Clinical findings
Spleen and liver
No or mild splenomegaly or hepatomegaly
Hematology (variable)
Mild anemia
Mild to moderate leukocytosis
Mild to marked thrombocytosis
Morphological findings
Blood
No or mild leukoerythroblastosis
No or mild red blood cell poikilocytosis
Few if any dacryocytes
Bone marrow
Hypercellularity
Neutrophilic proliferation
Megakaryocytic proliferation
Megakaryocytic atypia*
Minimal or absent reticulin fibrosis

*Clustering of megakaryocytes, abnormally lobulated megakaryocytic nuclei, naked megakaryocytic nuclei.

minimal or no demonstrable excess in reticulin fibers, that is, the prefibrotic or "cellular phase." Therefore, the demonstration of reticulin fibrosis, although characteristic, is not a required criterion for the diagnosis of PMF. Instead, the cardinal and therefore required features for PMF include increase in megakaryocyte growth associated with conspicuous abnormalities as well as granulocyte proliferation.[26] However, in the absence of reticulin fibrosis, meeting the first major criterion for PMF diagnosis requires, in addition to the aforementioned megakaryocyte changes, presence of bone marrow hypercellularity, granulocyte proliferation, and decrease in erythroid precursors.

The other two major criteria underline the need to exclude either myelofibrosis associated with another myeloid neoplasm (major criterion 2) or reactive bone marrow fibrosis (major criterion 3).

Table 6. 2001 WHO criteria for fibrotic stage primary myelofibrosis

2001 criteria for fibrotic PMF
Clinical findings
Spleen and liver
Moderate to marked splenomegaly or hepatomegaly
Hematology
Moderate to marked anemia
White blood cells decreased to elevated
Platelet count decreased to elevated
Morphological findings
Blood
Leukoerythroblastosis
Prominent red blood cell poikilocytosis
Prominent dacryocytosis
Bone marrow
Reticulin and/or collagen fibrosis
Decreased cellularity
Dilated marrow sinuses
Intraluminal hematopoiesis
Neutrophilic proliferation
Prominent megakaryocytic proliferation
Megakaryocytic atypia*
New bone formation (osteosclerosis)

*Clustering of megakaryocytes, abnormally lobulated megakaryocytic nuclei, naked megakaryocytic nuclei.

Table 7. Proposed revised WHO criteria for primary myelofibrosis

Proposed criteria for PMF
Major criteria
1. Presence of megakaryocyte proliferation and atypia,* usually accompanied by either reticulin and/or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)
2. Not meeting WHO criteria for PV,† CML,‡ MDS,§ or other myeloid neoplasm
3. Demonstration of *JAK2*617V>F or other clonal marker (eg, *MPL*515W>L/K), or in the absence of a clonal marker, no evidence of bone marrow fibrosis due to underlying inflammatory or other neoplastic diseases¶
Minor criteria
1. Leukoerythroblastosis‖
2. Increase in serum lactate dehydrogenase level‖
3. Anemia‖
4. Palpable splenomegaly‖

Diagnosis requires meeting all 3 major criteria and 2 minor criteria.

* Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.

† Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels. Red cell mass measurement is not required.

‡ Requires the absence of *BCR-ABL*.

§ Requires the absence of dyserythropoiesis and dysgranulopoiesis.

¶ Secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies. It should be noted that patients with conditions associated with reactive myelofibrosis are not immune to primary myelofibrosis and the diagnosis should be considered in such cases if other criteria are met,

‖ Degree of abnormality could be borderline or marked.

The former requires the absence of meeting WHO criteria for another myeloid neoplasm and the latter the demonstration that either *JAK2*617V>F (or other clonal markers such as *MPL*515W>L/K) is present or bone marrow fibrosis is not attributed to a nonclonal process like (chronic) toxic myelopathies due to a variety of exogenous agents, lymphoid neoplasms such as hairy cell leukemia and lymphoma, or a metastatic malignancy.[24] The diagnosis of PMF according to the revised WHO criteria requires meeting all 3 major criteria and, to increase diagnostic accuracy, in the context of prefibrotic/cellular phase disease, 2 of 4 minor criteria (Table 7).

The distinction between PMF on one hand, and MDS with fibrosis, ET, or acute panmyelosis with myelofibrosis (in many cases a hyperfibrotic subtype of acute myeloid leukemia [AML] according to the WHO),[32,33] on the other, requires careful morphologic assessment.[26,34] PMF is characterized by megakaryocytes that are often found in sizable loose to tight clusters and range in size from small to large with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei. Bare megakaryocytic nuclei are common.[35] In contrast, MDS is characterized by its classic dysmyelopoietic features. The dysplastic megakaryocytes seen in MDS are usually small and often have monolobated, hypolobated, or widely dispersed nuclei and are not usually found in large clusters (with the exception of some cases of fibrotic MDS) as are typical for MPD.[34] On the other hand, the presence of ringed sideroblasts, although seen frequently in MDS, may also be found in some cases of MPD, and therefore lacks diagnostic specificity.[36,37] Such contention is consistent with the demonstration of *JAK2*617V>F in a high proportion of cases with "refractory anemia with ringed sideroblasts and thrombocytosis (RARS-T)."[38-42] A proportion of these cases might "represent" true MPD cases (ET or PMF) with ringed sideroblasts.[43] Other cases, with more pronounced MDS-like abnormalities, such as dyserythropoiesis and anemia, might or might not

display additional morphologic abnormalities of megakaryocytes that resemble those seen in MPD.[38-42]

Careful bone marrow morphologic examination is crucial in distinguishing ET from prefibrotic PMF, an important detail that was overlooked by the original Polycythemia Vera Study Group (PVSG) criteria,[44,45] despite its potential confounding effect on both survival and rate of myelofibrotic transformation.[46] Such distinction takes into account the degree of bone marrow cellularity (marked hypercellularity in cellular-phase PMF), the presence of prominent granulocyte proliferation with left-shifted forms (typical in PMF but absent in ET), and in particular megakaryocyte morphology (with the aforementioned nuclear features in PMF and giant, mature-appearing megakaryocytes with deeply lobulated and hyperlobulated nuclei in ET).[17] Nevertheless, to reinforce diagnostic accuracy, the revised WHO diagnostic criteria for PMF require the presence of at least 2 of 4 PMF-characteristic peripheral blood or clinical features: leukoerythroblastosis, increased serum lactate dehydrogenase level, anemia, and palpable splenomegaly.

Patients with acute (malignant) myelofibrosis or panmyelosis with myelofibrosis usually present with severe constitutional symptoms, pancytopenia, and mild or no splenomegaly and feature an increase in blood and/or bone marrow blast count that will partially approach or fulfill the required threshold for AML diagnosis.[33] In this context, it has been shown that the latter is a heterogeneous entity that should be differentiated from AML[33] and MDS with accompanying myelofibrosis and a low blast count.[34,47] Nevertheless, in all cases with myelofibrosis, blasts may be difficult to accurately estimate, and CD34 assessment by immunohistochemistry may be invaluable in such cases.[48] Finally, the presence of either del(13)(q11~13q14~22) or der(6)t(1,6)(q21~23; p21.3) is strongly suggestive but not diagnostic for PMF.[49,50]

Conclusions

The proposed revisions to the diagnostic guidelines require the time-honored integration of clinical, laboratory, and pathologic findings. However, now the laboratory data include evaluation for a molecular defect, $JAK2$617V>F, that when present clearly identifies the process as neoplastic and thus eliminates the need for additional tests previously performed to exclude reactive myeloproliferation caused by other diseases. The revised criteria also take advantage of the recently appreciated contribution of specific morphologic abnormalities to the diagnosis of the MPDs. The histologic differences among the entities outlined here are recognized by experienced hematopathologists, and there is ongoing investigation to establish even more precise quantitative definitions similar to those established for other myeloid neoplasms.[51]

The objective of establishing diagnostic criteria is neither to capture all biologically true cases of disease nor guarantee 100% diagnostic specificity. For example, recent communications have disclosed the presence of $JAK2$617V>F in "idiopathic" abdominal vein thrombosis in patients who otherwise do not fulfill conventional diagnostic criteria for either PV or ET.[16] Some of these patients subsequently developed erythrocytosis and/or thrombocytosis, whereas others appear to have stable counts for many years. Regardless, such cases represent unclassified MPDs and should not be forced into a specific diagnosis, for research purposes. We provide this example to emphasize the point that not fulfilling a given set of published criteria does not prevent one from making a specific working diagnosis that is based on sound clinical judgment.

Authorship

Contribution: A.T., J.T., A.O., and J.W.V. prepared the initial draft of the proposals for revision of the WHO diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis. A.T. wrote the paper. J.T., A.O., and J.W.V. participated in the writing of the paper. All of the authors participated in the discussion and have reviewed and approved the current version of the manuscript.

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J.T. and J.W.V. are members of the Steering Committee for Revisions of the WHO Classification of Haematopoietic and Lymphoid Neoplasms.

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