The 2008 WHO Diagnostic Criteria for Polycythemia Vera, Essential Thrombocythemia, and Primary Myelofibrosis

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Several international working groups cooperated to propose new diagnostic guidelines for polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) to the steering committee of the World Health Organization. Because *JAK2* mutation status presents a decisive diagnostic test in PV, this feature was introduced as a major criterion. Minor criteria, such as characteristic bone marrow morphology, low erythropoietin level, and erythroid colony formation, were kept as supporting parameters. In PMF, major diagnostic criteria were established by histologic features independent of the presence of relevant fibrosis or myelofibrosis with myeloid metaplasia. *JAK2* mutation status was restricted to positive findings to exclude reactive myelofibrosis. A decrease in the platelet level was proposed for ET, because vascular complications may occur at lower platelet counts. As with PMF, morphology plays a distinctive role in diagnosis, particularly for its differentiation from early-stage PV or prodromal PMF associated with thrombocytosis.

Introduction

In the revised 2008 World Health Organization (WHO) classification system, the term *disease* is replaced by *neoplasm*, implying that the classic Philadelphia chromosome–negative (Ph^-) subtypes—polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF)—are now referred to as *myeloproliferative neoplasms* (MPNs) [1•]. The rationale for the diagnosis and classification of these clonal hematopoietic stem cell disorders, which are characterized by proliferation of one or more of the myeloid cell lineages, has been influenced by two main factors: the recent discovery of genetic abnormalities involved in the pathogenesis of Ph^- MPNs and the appreciation of specific histologic features correlating with clinical findings that are warranted as criteria to discriminate between MPN subtypes [2••]. Acquired somatic mutations of *JAK2*V617F [3••,4,5] and *JAK2* exon 12 [6,7] have been demonstrated to play a crucial role in the pathogenesis of many cases of Ph^- MPN [8•]. *JAK2*V617F mutation is detected in about 95% of patients with PV as a secondary genetic event that is preceded by a yet-undefined molecular abnormality [9•]. As a consequence of this mutation, transformation and proliferation of hematopoietic progenitor cells are promoted by downstream signal transduction pathways [3••,7]. It is very important to note that in ET and PMF, this mutation is found in only about 50% of patients [4,5,7] and that in *JAK2*V617F-negative PV, an activating *JAK2* exon 12 mutation is detectable [7], whereas in a small fraction of patients with ET or PMF, an activating mutation of *MPL*W515L/K is present [8•]. Moreover, it must be emphasized that *JAK2*V617F is not specific for any MPN, nor does its absence exclude any MPN.

For this reason, despite the recent progress in the molecular pathogenesis of MPNs, a synoptic approach, taking into account clinical, morphologic, and genetic features, remains the gold standard for classification aimed at a consensus-based working diagnosis [2••]. Concerning clinical and morphologic features, one should realize that MPNs display an insidious onset and stepwise progression comprising the full spectrum of prodromal and terminal stages, the latter terminating in bone marrow insufficiency, myelodysplastic changes, and blast crisis. In particular, precursor stages pose a number of problems because at onset they may not present with the classic clinical criteria for diagnosis and thus are recognizable

Table 1. The 2008 World Health Organization diagnostic criteria for polycythemia vera

Diagnosis requires meeting both major criteria and one minor criterion or the first major criterion and two minor criteria.

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*V617F 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.

*Hemoglobin or hematocrit > 99th percentile of method-specific reference range for age, sex, and altitude of residence; or hemoglobin > 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 cannot be attributed to correction of iron deficiency; or elevated red cell mass > 25% above mean normal predicted value.
(*Adapted from* Tefferi et al. [1•,2••].)

only by careful bone marrow examinations in combination with biologic tests and a positive mutation status, usually heralding the full-blown clinical presentation [8•]. Consequently, the diagnostic algorithms for PV, ET, and PMF have been substantially changed to include information regarding *JAK2*V617F status and similar activating mutations [1•,2••]. This review tries to highlight characteristic histologic features of bone marrow, characterizing the dynamics of the disease process correlated with relevant clinical data and mutation status as a useful means for a more elaborate diagnostic approach to establish the different categories of MPN [2••].

Polycythemia Vera

As already outlined, the rationale for the revision of the criteria for classifying MPNs was driven by new findings, particularly the discovery of the *JAK2*V617F mutation. The intention is to enhance clinicopathologic correlations, widening appreciation of the association between histologic bone marrow patterns and clinical data [1•,2••]. The optimal diagnosis of PV takes into account specific molecular, biologic, and morphologic features that are not present in either secondary or apparent PV [2••]. First, autonomous (true) polycythemia (ie, PV) must be differentiated from secondary and spurious forms by demonstrating an increased red cell mass (RCM) [10]. On the other hand, an increased hematocrit or hemoglobin level is not always consistent with a true increase in the RCM; PV occasionally may be masked by a normal-appearing hematocrit or hemoglobin value because of an associated increase in plasma cell volume with marked splenomegaly [11]. The Polycythemia Vera Study Group (PVSG) was a fervent advocate of the RCM measurement as the gold standard for diagnosis of PV, especially considering this shortcoming [10,12,13]. This practice was repeatedly used but now is widely neglected in many areas in favor of molecular, biologic, and histologic parameters [2••]. In the diagnostic algorithm shown in Table 1, the most valuable criterion of the molecular markers is the *JAK2*V617F mutation status, which is positive in nearly all patients [7,14,15], or other functionally similar aberrations, such as *JAK2* exon 12 mutation [6,7]. A very small number of negative PV cases have been described [8•]. However, current *JAK2*V617F mutation detection techniques are not always standardized and inconsistencies also may be created by the different tissue sources for test samples [8•]. To overcome these shortcomings, the revised WHO classification (Table 1) includes as concomitant (minor) criteria histopathology of the bone marrow, subnormal serum erythropoietin levels [16,17], and endogenous erythroid colony formation [8•,18]. These parameters are important when the two major criteria are not in agreement and are very helpful in detecting early or occult prepolycythemic stages of PV that may not present initially with a significant rise in the hemoglobin or hematocrit value, but present a frequent history of thrombosis [19,20], or a high platelet count mimicking essential thrombocythemia [21–23].

The histopathology of prepolycythemic PV and overt PV is usually characterized by hypercellular bone marrow due to a trilineage proliferation (panmyelosis) of erythroid and granulocytic precursors in variable proportions, associated with megakaryocytic growth including cells that display distinctive morphologic features [21,24,25]. Some of these findings are more significant than others in establishing the diagnosis of PV and in distinguishing it from reactive or secondary polycythemia (SP) and from the other types of MPNs [26,27]. In PV, the usually small and rounded islets of nucleated erythroid precursors are conspicuously enlarged and tend to merge into sheets. These changes are significantly more pronounced in PV, but they may also be expressed in a few cases with severe SP, so this feature alone is not a reliable diagnostic parameter, especially in the early stage of disease [24–27,28•]. A similar situation may be observed regarding the neutrophil cell lineage: an increase in promyelocytes and metamyelocytes (left-shifting) is seen frequently in PV and occasionally in SP. On the other hand, megakaryocytes in PV vary in size, often with large to giant cells (pleomorphous aspect) that are not found in SP [25,26,28•]. Altogether, careful histologic analysis of bone marrow features, including a set of relevant parameters, enables the diagnosis of PV (Table 2). The most common pattern of disease progression is post-polycythemic myelofibrosis (post-PV MF) accompanied by myeloid metaplasia, which is characterized by a leukoerythroblastic blood smear, poikilocytosis with teardrop-shaped

Table 2. Discriminating features generating histologic patterns in initially performed bone marrow biopsy specimens

			Primary myelofibrosis, %	
Feature*	**PV, %**	**ET, %**	**Prefibrotic/early stage**	**Overt fibrotic stage**
Increased cellularity (age-matched)	80–100	10–20	80–100	10–20
Neutrophil granulopoiesis				
Increased quantity	80–100	≤ 10	50–80	0
Left-shifting	50–80	≤ 10	20–50	10–20
Erythropoiesis				
Increased quantity	80–100	≤ 10	≤ 10	0
Left-shifting	80–100	≤ 10	10–20	≤ 10
Megakaryopoiesis				
Increased quantity	50–80	80–100	50–80	20–50
Size				
Small	20–50	0	20–50	20–50
Medium	20–50	10–20	10–20	10–20
Large	20–50	20–50	20–50	10–20
Giant	10–20	20–50	10–20	≤ 10
Histotopography				
Endosteal translocation	10–20	10–20	20–50	20–50
Cluster formation: Size				
Small (≥ 3)	10–20	10–20	50–80	50–80
Large (> 7)	≤ 10	0	20–50	20–50
Cluster formation: Quality				
Dense	≤ 10	0	20–50	50–80
Loose	20–50	20–50	50–80	10–20
Nuclear features				
Hypolobulation (bulbous/cloudlike)	10–20	≤ 10	50–80	50–80
Hyperlobulation (staghorn-like)	50–80	50–80	≤ 10	0
Maturation defects	0	0	50–80	80–100
Naked nuclei	20–50	20–50	50–80	80–100
Fibers				
Increased reticulin	10–20	0	50–80	80–100
Increased collagen	0	0	0	80–100
Osteosclerosis	0	0	0	20–50
Iron deposits	0	20–50	10–20	≤ 10
Lymphoid nodules present	10–20	0	10–20	≤ 10

*Semiquantitative evaluation (relative incidence): 0 = usually absent; ≤ 10% = rare; 10%–20% = slight; 20%–50% = moderate; 50%–80% = manifest; 80%–100% = overt.
ET—essential thrombocythemia; PV—polycythemia vera.

Table 3. The 2008 World Health Organization (WHO) diagnostic criteria for essential thrombocythemia

Diagnosis requires meeting all four criteria.

1. Sustained* platelet count ≥ 450 × 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 polycythemia vera,† primary myelofibrosis,‡ *BCR-ABL1*–positive chronic myelogenous leukemia,§ or myelodysplastic syndrome¶ or other myeloid neoplasms.
4. Demonstration of *JAK2*V617F or other clonal marker, or in the absence of *JAK2*V617F, no evidence for reactive thrombocytosis.**

*Sustained during the workup process.
†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, and red cell mass measurement is not required.
‡Requires the absence of relevant reticulin fibrosis, collagen fibrosis, peripheral blood leukoerythroblastosis, or markedly hypercellular marrow accompanied by megakaryocyte morphology that is typical for primary myelofibrosis (small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering).
§Requires the absence of *BCR-ABL1*.
¶Requires the 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 essential thrombocythemia if the first three criteria are met.
(*Adapted from* Tefferi et al. [1•,2••].)

red blood cells, and splenomegaly due to extramedullary hematopoiesis [29•]. The morphologic hallmark of this stage of the disease is overt reticulin and collagen fibrosis of the marrow [24,25,27]. The cellularity varies in this terminal stage, but hypocellular specimens are common. Clusters of megakaryocytes, often with hyperchromatic and very dysmorphic nuclei, are prominent. Erythropoiesis and granulopoiesis are decreased, and these cells are sometimes found, along with megakaryocytes, within dilated marrow sinusoids [24,25,27]. Osteosclerosis may also occur.

Essential Thrombocythemia

According to the PVSG, the formal diagnostic criteria for ET included a platelet count threshold of at least 600 × 10^9/L [12,13,30], significantly higher than the upper limits of the normal value (about 350 × 10^9/L) [1•,2••]. This arbitrarily established value could lead to an unintended oversight of prodromal stages of ET, especially those that present with relevant vascular complications at a far lower platelet count [20,31,32]. To recognize early and occult presentations, a lowering of the platelet count to 450 × 10^9/L seemed to be warranted and biologically sound [1•,2••]. As with polycythemic status, the diagnosis of ET requires differentiation from reactive thrombocytosis due to a variety of underlying conditions as well as clonal thrombocytosis associated with another MPN, especially PMF, *BCR-ABL1*–positive chronic myelogenous leukemia, and myelodysplastic syndromes presenting with a high platelet count (Table 3). Contrasting PV molecular markers are of limited value, because *JAK2*V617F mutation is detectable in only about 50% of patients [4,7,8•] and *MPL*W515L/K mutation is identified in a very small proportion [8•,33]. Therefore in addition to bone marrow examination and correlation with clinical data, the other subtypes of MPN must be excluded. Characteristic histologic bone marrow patterns offer a clue for the diagnosis of ET and are considered a major aid in establishing the diagnosis in *JAK2*V617F-negative patients. In bone marrow specimens of ET patients, usually neither a relevant increase in cellularity nor a significant left-shifted neutrophil granulopoiesis is observable. Any case with a mild to moderate granulocytic and erythroid growth pattern (panmyelosis) is suspicious for occult (prepolycythemic) PV mimicking ET [21]. Gross disturbances of the histologic topography involving significant abnormal localization or extensive dense clustering of megakaryocytes are not detectable. Megakaryocytes show a more or less random distribution within the bone marrow, with scattered forms or a few loose clusters. According to the WHO classification [1•,2••], a predominance of large to giant mature megakaryocytes with extensively folded (staghorn-like) nuclei [24,28•,34] surrounded by a correspondingly mature cytoplasma is found in ET. These features are clearly distinguishable from those of prefibrotic early PMF, in which megakaryocytes usually show extensive dense clustering and hypolobulated (cloudlike) and hyperchromatic nuclei with striking maturation defects that result in a marked anomaly of their nuclear-cytoplasmic ratio [34,35,36•,37]. Finally, at presentation, there is no substantial increase in reticulin fibers, and collagen fibrosis is never observable in ET (Table 2). The criteria of the PVSG, in contrast, allow some degree of fibrosis [12,13]. The lack of significant reticulin fibrosis has been reported in a large series of patients; minimal to slight myelofibrosis was described in only 3% of patients at onset [24]. All these features are relevant for recognition of the histologic pattern characterizing ET (Table 2). Evolution of disease features does include an insidious progression into post–ET myelofibrosis (post-ET MF) [29•] after 10 to 15 years in a few patients; this progression is associated with extramedullary hematopoiesis (myeloid metaplasia).

Primary Myelofibrosis

Overt presentations of PMF are characterized by the classic findings of anemia, splenomegaly, bone marrow fibrosis, and a leukoerythroblastic blood picture [38–40] consistent with myelofibrosis with myeloid metaplasia

Table 4. The 2008 World Health Organization (WHO) diagnostic criteria for primary myelofibrosis

Diagnosis requires meeting all three major criteria and two minor criteria.

Major criteria

1. Presence of megakaryocyte proliferation and atypia,* usually accompanied by 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 polycythemia vera,† *BCR-ABL1*+ chronic myelogenous leukemia,‡ myelodysplastic syndrome,§ or other myeloid neoplasms
3. Demonstration of *JAK2*V617F or other clonal marker (eg, *MPL*W515L/K), or in the absence of a clonal marker, no evidence that the bone marrow fibrosis or other changes are secondary to infection, autoimmune disorder, or other chronic inflammatory condition; hairy cell leukemia or other lymphoid neoplasm; metastatic malignancy; or toxic (chronic) myelopathies.¶

Minor criteria

1. Leukoerythroblastosis**
2. Increase in serum lactate dehydrogenase level**
3. Anemia**
4. Splenomegaly**

*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-ABL1*.
§Requires absence of dyserythropoiesis and dysgranulopoiesis.
¶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.
(*Adapted from* Tefferi et al. [1•,2••].)

(MMM) comparable to post-PV and post-ET MF [29•]. Neither bone marrow insufficiency associated with extramedullary hematopoiesis nor bone marrow fibrosis characterize PMF, for they can be encountered in a wide spectrum of clonal and nonclonal disorders. For this reason, the WHO classification scheme requires diagnostic histologic disease patterns to reveal the evolution of the disease process, starting with a prefibrotic stage and merging into the classic manifestation of MMM [1•,2••]. These criteria are combined with molecular findings (Table 4), although *JAK2*V617F mutation with relevant clinical data are positive in only 50% of the patients [5,7,8•] and the *MPL*515L/K mutation is found in a very small fraction [33,41]. The initial histopathologic findings in PMF are hypercellular bone marrow characterized by prominent granulocytic and megakaryocytic myeloproliferation with concomitant reduction and maturation arrest of the nucleated erythroid precursors, without (or with no more than a mild degree of) reticulin fibrosis (Table 2). Most conspicuous is the abnormal megakaryopoiesis, which is characterized not only by a disturbance of bone marrow histologic topography (extensive clustering of megakaryocytes with loose to dense groupings and abnormal localization of these towards the endosteal borders) but also by striking abnormalities in their morphology and maturation [42]. Significant megakaryocyte anomalies include a high degree of cellular pleomorphism, with variations in size from small to giant forms, and, in particular, abnormal nuclear foldings and an aberration of the nuclear cytoplasmic ratio created by large, bulbous, and hyperchromatic cloud-shaped nuclei. Furthermore, apart from their disorganized nuclear lobulation, many so-called naked (bare) megakaryocytic nuclei are detectable [28•,37,42]. Overall, the megakaryocytes in PMF regularly are characterized by a more pronounced degree of cytologic atypia (megakaryocytic dysplasia, dysmegakaryopoiesis) than in any other subtype of MPN, especially ET [34,35,36•,37,42,43]. Megakaryocytic dysplasia is thus one of the most important features discriminating prefibrotic, early-stage PMF (ie, false ET) from true ET, a concept that is also stressed by the WHO classification system (Table 2). Various studies have shown that there is more than 65% probability of progressing from a prefibrotic early stage to full-blown disease associated with clinical signs and symptoms of myeloid metaplasia conforming with the classic diagnostic criteria [37,44,45]. Unlike the initial prefibrotic or early (reticulin fibrotic) stages of PMF, the more advanced fibro-osteosclerotic phases of the disease (conforming with classic MMM) are characterized not only by a significant amount of reticulin deposition but, most importantly, by the appearance of coarse bundles of collagen fibers in the bone marrow (Table 2). Additional features indicating an advanced to terminal stage include plaque to budlike osteosclerosis (endophytic bone formation), which is often associated with patchy hematopoiesis replaced by adipose tissue (ie, progressive hypoplasia). Similar to the prodromal stages, atypical megakaryopoiesis (including the presence of numerous naked nuclei of megakaryocytes) remains a most prominent feature. Dilated marrow sinuses with intraluminal hematopoiesis, especially of megakaryocytes, are other prominent marrow findings [24,37,42,43].

Definition and Standardization of Bone Marrow Morphology in MPN

In the WHO classification [2••], the different subtypes of MPNs are characterized by specific histologic patterns of the bone marrow with distinctive features (Table 2) that should always be reviewed in context

with clinical data and mutation status, with the aim of achieving a consensus-based working diagnosis [8•]. A number of earlier studies have elaborated on these alterations [24,28•,42,43], but a conflict of opinion remains as to whether pathologists can recognize these features on routinely processed bone marrow sections, making possible a histology-based classification and diagnosis. Unlike the determination of age-dependent cellularity and semiquantitative grading of myelofibrosis [46], features characterizing megakaryopoiesis may cause significant difficulties in definition among different observers and consequently may hinder easy recognition. In this context, a systematic evaluation including the arrangement of the megakaryocytes within the bone marrow space (ie, histotopography) and certain nuclear abnormalities besides maturation defects may prove to be crucial [47]. In normal bone marrow, megakaryocytes show a central distribution of single isolated cells [34]. In MPN, the increase of megakaryocytes is often associated with the formation of small clusters (at least three cells) to extensive groups (more than seven cells). These megakaryocyte clusters may be arranged loosely (intermingled with other hematopoietic cells) or densely [47]. Moreover, an abnormal dislocation of megakaryocytes towards the endosteal (paratrabecular) border is a highly conspicuous finding that is usually not seen in reactive disorders. Other features indicating a neoplastic process are peculiar nuclear aberrations and maturation defects that imply disturbances of the normal development of megakaryopoiesis [28•,34,47]. These include atypical nuclear lobulation (extent and shape of nuclear foldings; ie, hypolobulation), often described as cloudlike, leading to bulbous (plump, clumsy) nuclei, versus hyperlobulation with marked segmentation (so-called staghorn-like formation) and anomalies of the chromatin pattern (mostly hyperchromasia). Maturation defects include a conspicuous deviation of the nuclear–cytoplasmic ratio or abnormal maturation with the appearance of bizarre megakaryocytes [47]. All these changes may be detectable in megakaryocytes of different sizes or ploidy status. Finally, so-called naked (denuded, bare) nuclei with a condensed chromatin pattern frequently implicate stimulated thrombocyte shedding and cell turnover. Of the other parameters, increase and left-shifting of neutrophil granulopoiesis or erythropoiesis may be a prominent feature, along with reduction in the amount of nucleated red cell precursors, depending on the disease entity (Table 2).

In this context, a more critical issue is the differentiation between ET and precursor stages of PMF with associated thrombocytosis, which often mimic ET clinically [34]. A recently published blinded study involving three hematopathologists questions the reproducibility and validity of distinguishing so-called true ET according to the WHO classification [2••] from prefibrotic PMF [48]. However, it should not be overlooked that the results of this study are greatly impaired by a number of significant inconsistencies, including lack of a training set for standardization, no clear definition of certain parameters (dysplastic or pyknotic megakaryocytes not defined by the WHO), small size of biopsies (≥ 0.5 cm rather than the required ≥ 1.5 cm) [46], the inability to reach a consensus on basic morphologic features such as erythroid cellularity, and no self-assessment (intraobserver evaluation). Moreover, in a considerable fraction of specimens, moderate to gross bone marrow fibrosis (grades 3 and 4 on a four-grade scale) [49] and new bone formation (osteosclerosis) were described, which do not characterize ET at onset, but are more in keeping with PMF [24,34,35,36•,37,42,43]. Apparently influenced by this study [48], an alternative perspective for the diagnostic approach to MPNs is offered in a very critical review paper with only marginal inclusion of bone marrow morphology [50], in substantial contrast to the rationales of the WHO classification [2••]. It is said that ''MPN marrow morphology is not only a moving target, but also nonspecific with respect to phenotype, in contrast to lymphomas and acute myeloid malignancies'' [50], a statement that is not in line with our experience and that of several other groups [24,28•,35,36•,37,43].

Conclusions

There has been major progress in the molecular/genetic classification of MPNs, and, as for chronic myelogenous leukemia, in Ph$^-$ MPNs the *JAK2*V617F mutation status and related aberrations may prove to be invaluable tools for molecular targeted therapy. According to the recent revision of the WHO classification, *JAK2*V617F mutation characterizes an MPN and presents a major diagnostic criterion for PV, but it is of only secondary diagnostic importance in ET and PMF. On the other hand, bone marrow morphology and associated clinical features are certainly warranted as yardsticks for diagnosis. It should be kept in mind that the main essence of the 2008 WHO diagnostic criteria for MPNs is the establishment of a clinically useful interface between hematologic data, histologic features, and molecular findings to achieve a consensus-based working diagnosis.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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