CME/SAM

Reproducibility of Histologic Classification in Nonfibrotic Myeloproliferative Neoplasia

Suzanne M. Koopmans, MD,[1] Freek J. Bot, MD, PhD,[1,2] King H. Lam, MD, PhD,[3] Arienne M.W. van Marion, MD, PhD,[1,4] Hendrik de Raeve, MD, PhD,[5] and Konnie M. Hebeda, MD, PhD[6]

Key Words: Myeloproliferative neoplasia; World Health Organization; Reproducibility; Histologic studies; Megakaryocyte morphologic features

DOI: 10.1309/AJCP2UG9SGGWAHUA

Upon completion of this activity you will be able to:
- list histologic criteria in the 2008 WHO system for diagnosis of myeloproliferative disorders.
- discuss challenges in reproducibility of diagnostic categorization and to cite those histologic features that are most and least reproducibly applied by pathologists examining bone marrow core biopsies.
- summarize strengths and limitations of histologic assessment in accurately classifying myeloproliferative disorders using the 2008 WHO system.

The ASCP is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The ASCP designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™ per article. Physicians should claim only the credit commensurate with the extent of their participation in the activity. This activity qualifies as an American Board of Pathology Maintenance of Certification Part II Self-Assessment Module.

The authors of this article and the planning committee members and staff have no relevant financial relationships with commercial interests to disclose.

Questions appear on p 656. Exam is located at www.ascp.org/ajcpcme.

Abstract

Early phases of polycythemia vera, essential thrombocythemia, and primary myelofibrosis (PMF) can be difficult to distinguish by morphologic studies alone because they share many morphologic characteristics. Histologic criteria according to the 2008 World Health Organization (WHO) classification are part of the myeloproliferative neoplasia (MPN) diagnosis. Our aim was to assess the reproducibility of morphologic characteristics and determine their relative importance for histologic diagnoses on selected trephine biopsy sections.

For the study, 56 prefibrotic MPN trephine specimens were blindly reviewed by 4 hematopathologists using a scoring list of 16 histologic characteristics mentioned in the WHO classification. Consensus was defined as agreement by 3 of 4 hematopathologists.

High degrees of consensus were reached for individual major morphologic features used in the WHO classification, especially for the nuclear features of megakaryocytes (83%). Some of the features correlated positively or negatively with the histologic diagnosis of PMF. Consensus for the histologic classification of MPN was reached in 39 (70%) of 56 cases without knowledge of clinical data. This finding indicates a difference in the relative importance assigned to individual histologic characteristics by different hematopathologists.

Myeloproliferative neoplasms (MPNs) are clonal bone marrow stem cell disorders originating from a multipotent hematopoietic stem cell. MPNs are characterized by the proliferation of 1 or more lineages of myeloid, erythroid, and megakaryocytic cells, resulting in increased numbers of granulocytes, erythrocytes, or platelets in the peripheral blood. According to the 2008 World Health Organization (WHO) criteria, MPNs can be divided into chronic myelogenous leukemia carrying the Philadelphia chromosome (Ph+) as a result of t(9;22), resulting in the *BCR-ABL1* fusion gene, and diseases that do not carry the Ph chromosome (Ph–).[1] The 3 most commonly occurring so-called classical Ph– MPNs are polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).[2,3]

In 1967, the Polycythemia Vera Study Group (PVSG) initiated extensive studies of PV. The diagnostic criteria were updated several times during the following decades and are widely used by hematologists. However, the appropriate use of the histologic studies of bone marrow biopsy (BMB) specimens as a diagnostic tool was neglected. To stress the relevance of a BMB, the WHO added a set of histologic diagnostic criteria in 2001.[4] The recent discovery of the *JAK2*^{V617F} mutation and the recognition of prefibrotic PMF resulted in the 2008 WHO classification of MPNs.[1,5-7]

PV is characterized by a proliferation of the 3 major hematopoietic cell lineages, usually resulting in increased numbers of circulating erythrocytes and often also leukocytes and blood platelets. The bone marrow features of PV are trilinear hypercellularity, loose clusters of a range of small to giant megakaryocytes, and, sometimes, a slightly increased amount of reticulin fibrosis.

The typical features of ET are thrombotic and hemorrhagic complications due to the proliferation of the megakaryocytic cell line, resulting in thrombocythemia. The bone marrow is characterized by increased numbers of loosely clustering, giant, hyperlobulated megakaryocytes with staghorn-like features and a lack of reticulin fibrosis. Erythropoiesis and myelopoiesis are typically not involved.

The bone marrow of patients with PMF is characterized by a proliferation of the megakaryocytic and, less conspicuously, granulocytic cell lineages. The megakaryocytes often demonstrate dense clustering and a large range in cell size, including giant megakaryocytes. Their nuclei demonstrate atypical features such as a cloud-like aspect, hypolobulation, irregular nuclear outlines, and hyperchromatic chromatin. During the course of the disease, the amount of reticulin fibrosis increases, finally resulting in collagen fibrosis with osteosclerosis.[3,8]

Early phases of PV, ET, and PMF share many morphologic characteristics and, consequently, can be difficult to distinguish from each other when using only histologic evaluation. Reliably distinguishing these 3 MPN subtypes in the early phase is important because of a different risk of thromboembolic complications of PV and the worse survival rate in PMF compared with ET, which is associated with a normal life expectancy.[1,9]

The first aim of this study was to assess the reproducibility of the major individual morphologic characteristics described in the WHO classification for the different prefibrotic MPNs. The other aims were to assess the reproducibility of the histologic diagnosis using only morphologic characteristics without knowledge of the clinical data and to gain insight into interpathologist differences.

Materials and Methods

Bone Marrow Trephine Specimens

Diagnostic BMB specimens from 56 consecutive patients diagnosed between 2001 and 2006 as having nonfibrotic ET (n = 30) or PV (n = 26) according to the PVSG criteria were retrieved from the files of the University Hospital Antwerp, Antwerp, Belgium. Bone marrow trephine biopsy specimens from all patients were routinely embedded in paraffin, and the original diagnostic sections were used for this study. The sections had been stained with H&E, periodic acid–Schiff, and Gomori silver impregnation to evaluate the morphologic features and reticulin fiber content.

Assessment of Bone Marrow Trephine Slides

The 56 trephine specimens were blindly reviewed by 4 pathologists (F.J.B., K.H.L., A.M.W.M., and K.M.H.) from different hospitals with a special interest in MPNs. Each pathologist assessed the trephine specimens independently and without knowledge of patients' age, sex, or any other clinical data and without knowledge of the original diagnosis.

For the study, 16 histologic characteristics, mainly related to megakaryocyte morphologic features, were previously agreed on and were scored for each case. An arbitrary threshold of at least 10% within the cells of a lineage was accepted, although the WHO classification does not give any quantitative criteria. Deliberately, no detailed agreement on the criteria was sought beforehand to establish whether there was consensus in the use of the WHO 2008 histologic criteria in daily practice.

Megakaryocyte nuclei were scored as staghorn, cloud-like, dysmorphic, or bare nuclei. The nuclear lobulation of the megakaryocytes was scored as normal, hyperlobulation, or hypolobulation. The clustering was divided into no clustering, loose clustering, or dense clustering. The cytoplasm of the megakaryocytes was recorded as normal, small, large, or dysmorphic. Additional features were dilated sinusoids and the myeloid/erythroid ratio (M/E ratio) **Table 1**. Definitions of the morphologic features are given in **Table 2**.

The histologic diagnosis was made according to the WHO 2008 criteria.[1] The diagnosis was no MPN or MPN, and, if possible, was further classified as ET, PV, or PMF. Although essential for the final diagnosis of the MPN, we did not record the clinical and laboratory data because this study was about measuring the interobserver variation in evaluating

Table 1
Degree of Consensus for 16 Histologic Characteristics in 56 Cases of Myeloproliferative Neoplasia*

Characteristic	Present	Absent
Megakaryocyte nuclei		
Staghorn	53 (95[88.6-100.6])	3 (5 [–0.6 to 11.5])
Cloud-like	48 (86 [76.0-95.5])	8 (14 [4.5-24.1])
Naked	477 (84 [73.8-94.0])	9 (16 [6.0-26.2])
Dysmorphic	46 (82 [71.4-92.9])	10 (18 [7.1-28.6])
Lobulation		
Normal	50 (89 [79.3-99.3])	6 (11 [0.8-20.7])
Hyperlobulated	48 (86 [74.9-96.6])	8 (14 [3.4-25.1])
Hypolobulated	42 (75 [61.9-88.1])	14 (25 [11.9-38.1])
Clustering		
Normal	41 (73 [60.0-86.5])	15 (27 [13.5-40.0])
Loose	40 (71 [57.8-85.1])	16 (29 [14.9-42.2])
Dense	49 (88 [78.0-97.0])	7 (13 [3.0-22.0])
Megakaryocyte cytoplasm		
Normal	42 (75 [63.2-68.8])	14 (25 [13.2-36.8])
Small	45 (80 [68.6-92.1])	11 (20 [7.9-31.3])
Large	50 (89 [80.7-97.6])	6 (11 [2.1-19.3])
Dysmorphic	43 (77 [63.7-89.9])	13 (23 [10.1-36.3])
Other features		
Dilated sinusoids	48 (86 [75.5-95.9])	8 (14 [4.1-24.5])
Myeloid/erythroid ratio	40 (71 [59.6-83.3])	16 (29 [16.7-40.4])
Diagnosis (myeloproliferative neoplasia type)	39 (70 [57.6-81.3])	17 (30 [18.3.-42.4])

* Values are given as number of cases (percentage [95% confidence interval]).

DOI: 10.1309/AJCP2UG9SGGWAHUA

Table 2
Definitions of Morphologic Features

Morphologic Feature	Definition
Staghorn nuclei	Large cells with deeply lobulated nuclei surrounded by mature cytoplasm
Cloud-like nuclei	Enlarged, bulbous, plump nuclei with decreased amount of cytoplasm
Naked nuclei	Compact hyperchromatic megakaryocyte nuclei without visible cytoplasm
Dysmorphic nuclei	Hyperchromatic nuclei with bizarre shapes
Hyperlobulation	>6 nuclear lobules; lobules often completely separated by cytoplasm
Hypolobulation	<4 nuclear lobules surrounded by ample mature cytoplasm
Dense clustering	At least 4 megakaryocytes lying back-to-back without being separated by other cells
Loose clustering	Dispersed cluster of at least 3 megakaryocytes without close contact
Small megakaryocyte cytoplasm	Megakaryocytes <4 myeloid cells in largest dimension
Large megakaryocyte cytoplasm	Megakaryocytes >8 myeloid cells in largest dimension
Dysmorphic megakaryocyte cytoplasm	Small to large megakaryocytes with abnormal nuclear/cytoplasmic ratio and a shape other than round
Dilated sinusoids	Visible sinusoids that may or may not be filled with hematopoietic cells
Myeloid/erythroid ratio	Ratio of estimated numbers of myeloid and nucleated erythroid cells

the histologic features used in the WHO 2008, irrespective of the clinical and laboratory data.

Consensus was defined as agreement by 3 of 4 pathologists. For statistical analysis Excel (Microsoft, Redmond, WA) was used to calculate the percentage of consensus and the confidence intervals.

To study the relative importance of the individual morphologic features for the diagnosis, we analyzed their reported frequency in PMF and non-PMF cases for each pathologist. Features that were reported as present in at least 75% of these cases or in fewer than 25% were considered of diagnostic importance and potentially able to discriminate between the 2 groups.

Results

Each pathologist scored the presence of 16 histologic characteristics and made a histologic diagnosis according to the WHO criteria. Some examples are shown in **Image 1**. As the scoring data show in Table 1, variation in the degree of consensus was found in the scoring of the 16 histologic characteristics, varying from 95% for the nuclear aspect staghorn to 71% for the presence of loose clustering of megakaryocytes. The degree of consensus for the nuclear features of the megakaryocytes was relatively high (at least 75% for hypolobulation), and the consensus for megakaryocyte cytoplasmic characteristics such as large and small was slightly lower. Also, the consensus for dense clustering (88%) was comparably high in comparison with loose clustering and no clustering (71% and 73%, respectively). Of the other characteristics, the M/E ratio showed lower consensus (71% [40/56]); of these 40 cases, 2 (5%) of 40 were diagnosed as erythroid hyperplasia and 37 (93%) of 40 as having a normal M/E ratio, and in 1 (3%) of the 40 cases, there was consensus about the presence of myeloid hyperplasia. As expected, the degree of consensus for the histologic diagnosis of MPN was 100% (56/56).

The confidence intervals are given in Table 1 along with the degree of consensus for the 16 histologic characteristics. The confidence interval has a comparable range for most morphologic features.

The consensus frequency for the histologic diagnosis of the various subtypes was 80% (45/56) for PMF, 20% (11/56) for PV, and 0% (0/56) for ET. PV was considered by at least 1 pathologist in 24 (43%) and ET in only 7 (13%) of the 56 trephine specimens.

The features that were present in at least 75% of the PMF cases were large megakaryocytes, small megakaryocytes, hyperlobulation, and a normal M/E ratio. Erythroid hyperplasia was reported in fewer than 25% of the PMF cases. In the non-PMF cases, no single feature was reported in more than 75%, but dysmorphic nuclei and megakaryocytes, dense clustering, dilated sinusoids, and myeloid hyperplasia were generally absent (<25%). Because myeloid hyperplasia, staghorn nuclei, and normal lobulation were reported in fewer than 25% of cases in both groups, they were not useful for discrimination **Table 3**.

Discussion

In this study, trephine biopsy specimens from 56 patients initially diagnosed as having a nonfibrotic MPN were blindly and independently reviewed by 4 hematopathologists using a scoring system of 16 histologic characteristics. The degree of consensus was relatively high for the overall nuclear features of the megakaryocytes (83%), calculated as the mean of the 10 nuclear features of the megakaryocytes. Especially the degree of consensus for the aspect of the megakaryocyte nuclei was high. These findings indicate that there is rather good agreement among hematopathologists concerning the definition of morphologic features.

DOI: 10.1309/AJCP2UG9SGGWAHUA

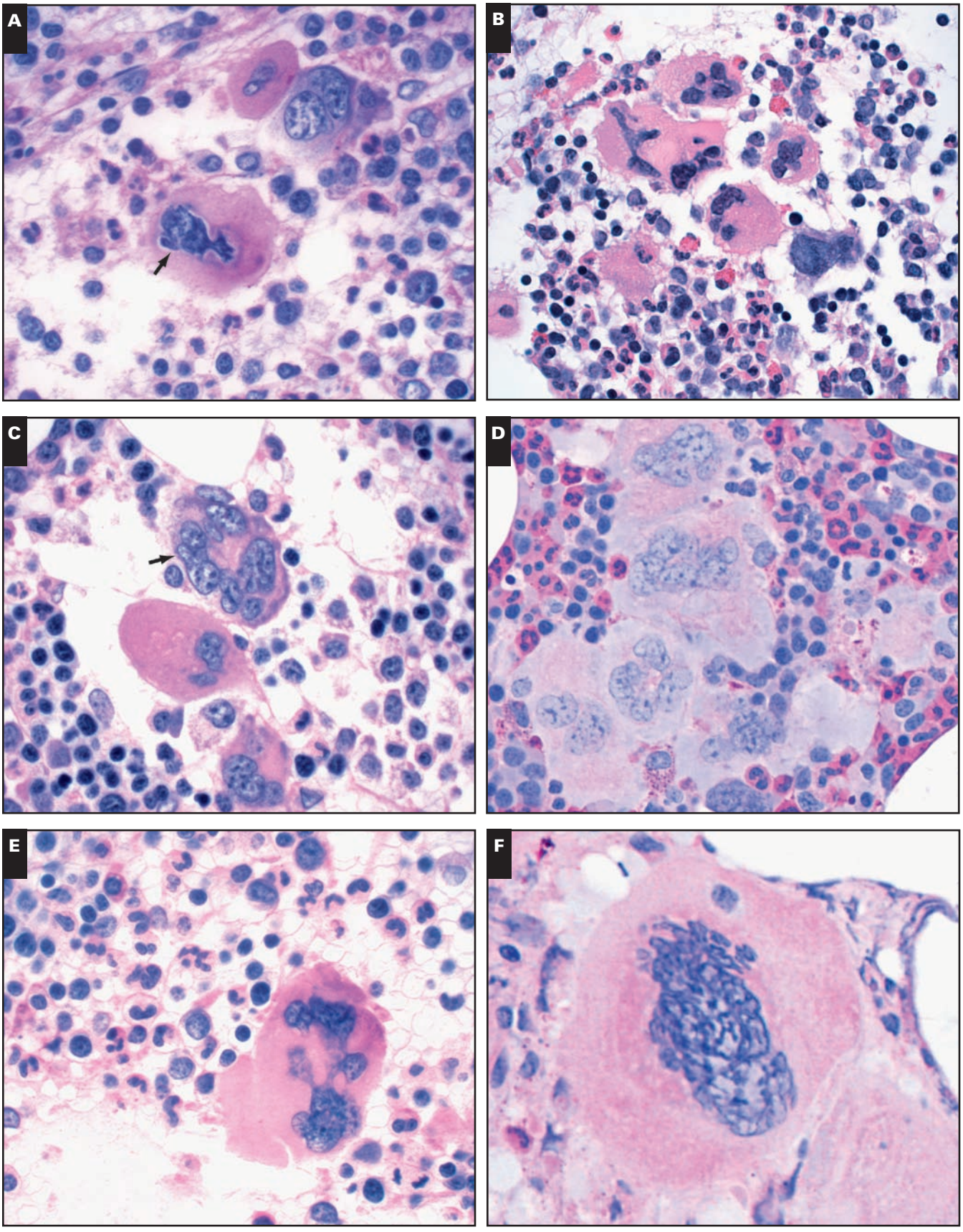

Image 1 Morphologic features of megakaryocytes scored on 54 bone marrow trephine specimens. **A**, Dysmorphic nucleus (arrow; H&E, ×200). **B**, Loose clustering (H&E, ×100). **C**, Hyperlobulated and enlarged nuclei (arrow; H&E, ×200). **D**, Dense clustering (periodic acid–Schiff, ×100). **E**, Staghorn nucleus (H&E, ×1,000). **F**, Cloud-like nucleus (H&E, ×1,000).

DOI: 10.1309/AJCP2UG9SGGWAHUA

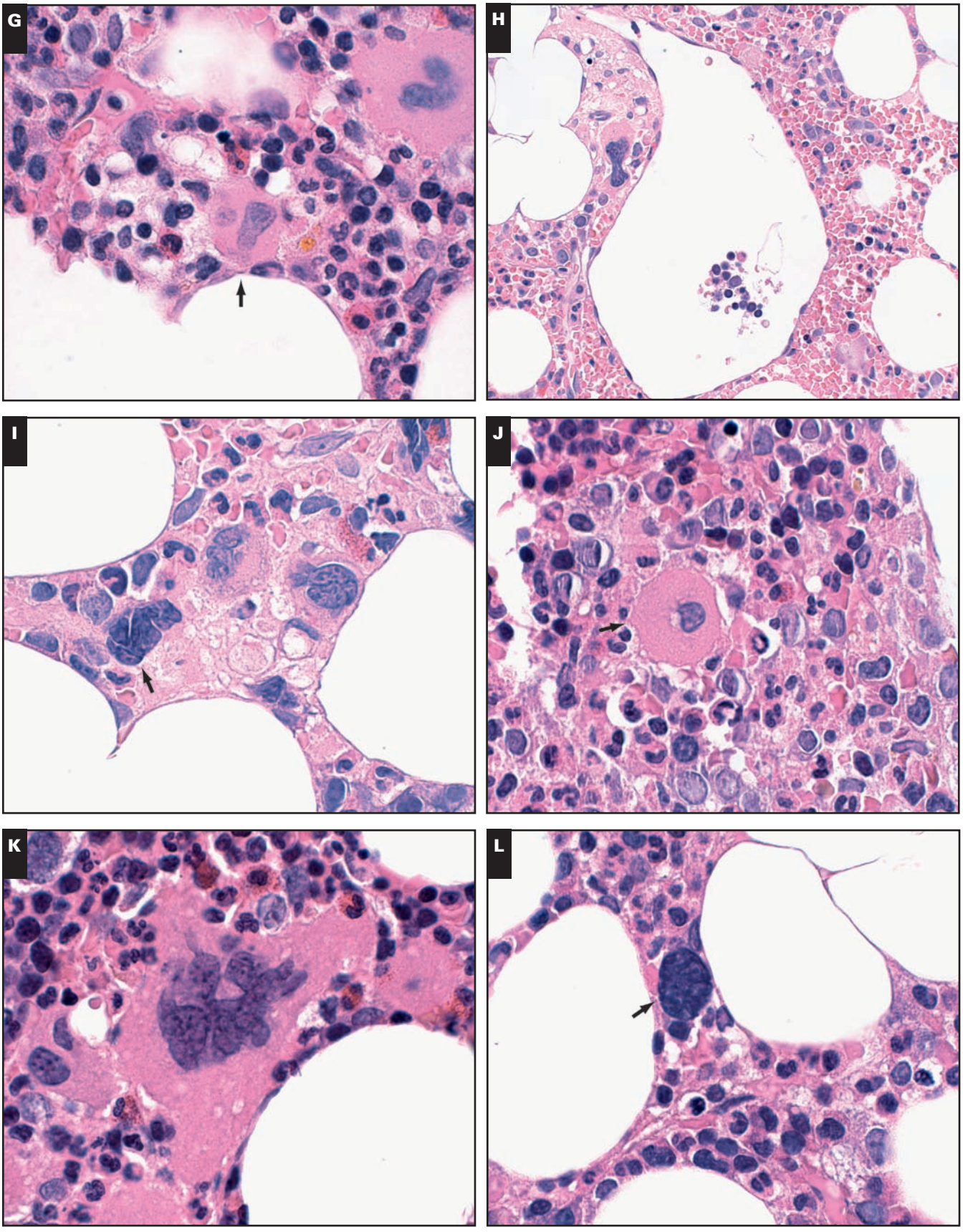

Image 1 (cont) **G**, Small megakaryocyte cytoplasm (arrow; H&E, ×1,000). **H**, Dilated sinusoids (H&E, ×100). **I**, Dysmorphic megakaryocyte (arrow; H&E, ×1,000) **J**, Hypolobulated nuclei (arrow; H&E, ×1,000). **K**, Large megakaryocyte cytoplasm (H&E, ×1,000). **L**, Naked megakaryocyte nuclei (arrow; H&E, ×1,000).

DOI: 10.1309/AJCP2UG9SGGWAHUA

Table 3
Morphologic Features Recorded by Four Pathologists in <25% or >75% of Cases Considered as PMF Compared With Non-PMF*

	PMF	Non-PMF
Frequent in PMF		
Small megakaryocyte cytoplasm	101/134 (75)	46/72 (64)
Large megakaryocyte cytoplasm	107/134 (80)	43/69 (62)
Hyperlobulation	97/129 (75)	48/71 (68)
Normal myeloid/erythroid ratio	100/133 (75)	43/78 (55)
Dysmorphic nuclei	53/130 (41)	12/71 (17)
Dysmorphic megakaryocytes	61/136 (45)	18/71 (25)
Dense clustering	59/134 (44)	9/55 (16)
Rare in non-PMF		
Dilated sinusoids	48/137 (35)	13/71 (18)
Rare in PMF		
Erythroid hyperplasia	7/140 (5)	28/62 (45)
Staghorn	12/122 (10)	5/61 (8)
Normal lobulation	13/122 (11)	18/83 (22)
Nondiscriminatory		
Myeloid hyperplasia	27/138 (20)	0/0 (0)

PMF, primary myelofibrosis.
* Data are given as number/total (percentage).

With the clinical PVSG criteria, prefibrotic PMF was not recognized as a separate entity and was classified as ET or PV. These criteria resulted in a relatively high frequency of ET owing to the presence of thrombocythemia that can occur in prefibrotic MPN. In our study, the use of the 2008 histologic WHO criteria led to a higher frequency of PMF (80%) and a lower frequency of PV (20%), and none of the trephine specimens were diagnosed as ET by consensus; ET was considered in only 13% of the trephine specimens. In line with our study, similar results were found by Gianelli et al[10] when they used the WHO criteria to reclassify patients with ET as diagnosed by the PVSG criteria. They found that the diagnosis for only 19% of the patients remained as ET, whereas the great majority of patients were rediagnosed as having PMF. Comparable data were found by Thiele and Kvasnicka[11] and Florena et al.[12]

It seems from this and other studies that the clinical manifestations of ET, prefibrotic PMF, and early fibrotic PMF are quite similar and that the clinical relevance of the subclassification cannot always be demonstrated.[10,11,13,14]

Samuelson et al[14] questioned in a letter to the editor whether there is sufficient confidence that evaluation of megakaryocyte morphologic features and fibrosis is widely reproducible among various observers. The study by Wilkins et al[9] supports this concern. Although individual morphologic features such as megakaryocyte lobulation, size, and clustering, which are important features for differentiating MPNs, show an acceptable degree of consensus by pathologists, this might be insufficient for daily practice in diagnosing MPN subtypes and predicting the differences in clinical outcome and prognosis, especially without further information on the thresholds and weight of these features. As shown in Table 1, consensus was particularly low for the characteristic megakaryocyte clustering, except for dense clustering. This finding indicates differences in the perception of loose clustering.

Loose clusters of megakaryocytes are considered a feature of ET and PV,[1] but apparently it is difficult to distinguish loose clusters from no clusters, thus leaving only dense clusters as a discriminatory feature. In our study, dense clustering was scored only in PMF, indicating its weight in diagnosing PMF. Wilkins et al,[9] on the other hand, found it more difficult to distinguish between loose clusters and dense clusters, and, in their study, the type of clusters showed a low strength of association. From that finding and our findings, it can be concluded that the aspect of clustering of megakaryocytes is difficult to apply reproducibly and that there is a need for providing criteria for determining the type of clustering.

Gianelli et al[10] showed that the recognition of dysmorphic megakaryocytes is important, demonstrating that besides dense clustering, dysmorphic features of the megakaryocytes discriminate nonfibrotic PMF from ET. Also, in our data, dysmorphic megakaryocytes were scored only in PMF, indicating specific importance in PMF. A low degree of consensus was reached for especially normal megakaryocyte size. The size of the megakaryocytes showed a more acceptable degree of consensus, 80%, but it varied from 75% for normal megakaryocyte size to 89% for large megakaryocytes. The low consensus for normal megakaryocytes is partly due to inconsistency in scoring by some of the pathologists: in case of abundant abnormal megakaryocytes, the presence of small numbers of normal megakaryocytes was not always recorded.

Megakaryocytic lobulation showed comparable results, with the degree of consensus of 83%. Hyperlobulation was one of the most commonly scored characteristics in PMF, as was hypolobulation in non-PMF cases, indicating its importance. For the M/E ratio, there was a 71% degree of consensus, and of these cases, 93% were diagnosed as having a normal M/E ratio. As depicted in the WHO 2008 criteria, the recognition of a significant degree of granulocytic proliferation is important to distinguish PMF from ET.[5] In our study 80% were rediagnosed as PMF; however, in only 3% of these cases was there consensus on myeloid hyperplasia. Also, the normal M/E ratio was 1 of the 4 average characteristics scored in PMF. This indicates that granulocytic proliferation is not considered a prerequisite for the diagnosis of PMF; other criteria or combined features were judged to be more important in reaching a diagnosis of PMF.

As one can expect, each morphologic feature makes a different contribution to each diagnosis. The numbers in our study were too small for a confident determination of their relative importance. From the reported frequency in PMF and non-PMF cases, we have at least some information on their

DOI: 10.1309/AJCP2UG9SGGWAHUA

assigned importance. Features that are considered as major histologic criteria for PMF by the WHO are small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering (Table 2.04 from Swerdlow et al[1]). In this study, these features were frequently reported in PMF (large megakaryocytes, small megakaryocytes) or rarely reported in cases diagnosed as non-PMF (dysmorphic nuclei and megakaryocytes, dense clustering). These findings indicate that the latter criteria are specific but apparently not sensitive enough to exclude PMF on their own in individual cases.

The aims of this study were to assess the reproducibility of the morphologic characteristics that are used in the WHO 2008 classification and to determine their relative importance for histologic diagnosis on selected trephine biopsy sections without knowledge of the clinical data. The independence of the clinical data in this study is important because the histologic picture is a major criterion for PMF, a necessary criterion for ET, and a minor criterion for PV. Moreover, in daily practice, recognition of a myeloproliferative disorder and histologic subtyping have to be performed quite often without all required clinical data to reach a final histologic diagnosis.[5,6]

Our study showed a high degree of consensus for individual histologic features that are described in the WHO classification of MPN BMB specimens, especially concerning megakaryocytic characteristics. The translation to a final histologic diagnosis is more problematic because, besides the recognition of individual histologic features, also their frequency, ranking, and combination have a role. Future diagnostics for MPN will increasingly integrate clinical and morphologic methods with genetic and protein expression data. A good example is the incorporation of *JAK2* mutation status in MPN diagnostics. However, at least for the time being, histologic assessment of a trephine biopsy specimen remains a tool for the subclassification of MPNs in daily clinical practice and in clinical trials.

From the Departments of Pathology, [1]University Hospital Maastricht, Maastricht, the Netherlands; [2]Haga Hospital, The Hague, the Netherlands; [3]Erasmus MC Rotterdam, Rotterdam, the Netherlands; [4]VieCuri Medical Center, Venlo, the Netherlands; [5]University Hospital Antwerp, Antwerp, Belgium; and [6]Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

Address reprint requests to Dr Koopmans: Dept of Pathology, University Hospital Maastricht, PO Box 616, 6200 MD Maastricht, the Netherlands.

Dr Koopmans collected and analyzed data, performed statistical analysis, interpreted data, and wrote the manuscript; Drs Bot, Lam, and van Marion contributed equally to the design of the study, the interpretation and scoring of the bone marrow trephine biopsy specimens, and writing of the manuscript; Dr de Raeve provided the trephine biopsy specimens; and Dr Hebeda designed the research, interpreted data, scored bone marrow trephine biopsy specimens, and wrote the manuscript. All authors had the opportunity to contribute to the drafting of the manuscript.

Acknowledgments: We gratefully thank R.-J. Koopmans for support with statistical analysis and acknowledge the contribution of J.J. Michiels, MD, PhD, in collecting the trephine biopsy specimens and raising critical questions on the histologic assessment of myeloproliferative neoplasia.

References

1. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press; 2008.
2. Campbell PJ, Green AR. The myeloproliferative disorders. *N Engl J Med*. 2006;355:2452-2466.
3. Murray J. Myeloproliferative disorders. *Clin Med*. 2005;5:328-332.
4. Jaffe ES, Harris NL, Stein H, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2001.
5. Tefferi A, Thiele J, Orazi A, et al. 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. *Blood*. 2007;110:1092-1097.
6. Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. *Leukemia*. 2008;22:14-22.
7. Turkington RC, Arnold EC, Percy MJ, et al. Comparison of diagnostic criteria for polycythaemia vera. *Hematology*. 2007;12:123-130.
8. Michiels JJ, Bernema Z, Van Bockstaele D, et al. Current diagnostic criteria for the chronic myeloproliferative disorders (MPD) essential thrombocythemia (ET), polycythemia vera (PV) and chronic idiopathic myelofibrosis (CIMF). *Pathol Biol (Paris)*. 2007;55:92-104.
9. Wilkins BS, Erber WN, Bareford D, et al. Bone marrow pathology in essential thrombocythemia: interobserver reliability and utility for identifying disease subtypes. *Blood*. 2008;111:60-70.
10. Gianelli U, Vener C, Raviele PR, et al. Essential thrombocythemia or chronic idiopathic myelofibrosis? a single-center study based on hematopoietic bone marrow histology. *Leuk Lymphoma*. 2006;47:1774-1781.
11. Thiele J, Kvasnicka HM. Chronic myeloproliferative disorders with thrombocythemia: a comparative study of two classification systems (PVSG, WHO) on 839 patients. *Ann Hematol*. 2003;82:148-152.
12. Florena AM, Tripodo C, Iannitto E, et al. Value of bone marrow biopsy in the diagnosis of essential thrombocythemia. *Haematologica*. 2004;89:911-919.
13. Brousseau M, Parot-Schinkel E, Moles MP, et al. Practical application and clinical impact of the WHO histopathological criteria on bone marrow biopsy for the diagnosis of essential thrombocythemia versus prefibrotic primary myelofibrosis. *Histopathology*. 2010;56:758-767.
14. Samuelson SJ, Parker CJ, Prchal JT. Revised criteria for the myeloproliferative disorders: too much too soon [letter]? *Blood*. 2008;111:1741-1742.

DOI: 10.1309/AJCP2UG9SGGWAHUA