Straightforward Identification of Masked Polycythemia Vera Based on Proposed Revision of World Health Organization Diagnostic Criteria for *BCR-ABL1*-Negative Myeloproliferative Neoplasms

Daehyun Chu, M.D., Young-Uk Cho, M.D., Seongsoo Jang, M.D., Eul-Ju Seo, M.D., and Chan-Jeoung Park, M.D.

Department of Laboratory Medicine, University of Ulsan, College of Medicine and Asan Medical Center, Seoul, Korea

Dear Editor

Some cases of polycythemia vera (PV) may mimic essential thrombocythemia (ET) owing to prominent thrombocytosis [1]. A recently proposed revision of the WHO diagnostic criteria for *BCR-ABL1*-negative myeloproliferative neoplasms (MPNs) has highlighted the diagnostic pitfalls of these cases and reintroduced the clinical entity of "masked" PV, which has been identified in patients with anemia or patients whose polycythemia was initially masked by thrombocytosis [2-4]. We speculated that a small number of masked PV patients might have been diagnosed initially as having ET on the basis of such findings as thrombocytosis, presence of *JAK2* mutation, elevated megakaryocyte count, and normal serum erythropoietin (EPO) level.

We reviewed the hematologic data of 84 patients diagnosed as having ET between January 2003 and April 2013, who were available for assessment of *JAK2*, *MPL*, and *CALR* mutational status. We found 11 (13.1%) patients with Hb or Hct levels between those in the WHO 2008 criteria and those in the proposed 2014 criteria (Hb >16.5 g/dL to 18.5 g/dL or Hct >49% for men, and Hb >16 g/dL to 16.5 g/dL or Hct >48% for women; Table 1). All 11 patients had the *JAK2* V617F mutation but neither the *MPL* nor the *CALR* mutation, which suggested that they might have the features of PV. We then reviewed bone marrow (BM) histomorphology and identified two (2.4%) patients who fulfilled the proposed revision of criteria for PV.

Patient 1 was a 36-yr-old man. His laboratory data included the following: leukocytes, 12.3×10^9/L; Hb, 17.6 g/dL; platelets, 577×10^9/L; and normal serum EPO level. The difference between baseline (16.5 g/dL) and pathologic Hb levels was less than 2 g/dL. He had been diagnosed as having ET and received anagrelide therapy. Two months later, he was also diagnosed as having non-ST-segment elevation myocardial infarction (NSTEMI) and underwent off-pump coronary artery bypass.

Patient 2 was a 63-yr-old man who had received a drug-eluting coronary stent for NSTEMI approximately two years earlier. He had thrombocytosis one year earlier. His laboratory data included the following: leukocytes, 19.3×10^9/L; Hb, 17.9 g/dL; and platelets, $1,577 \times 10^9$/L. A serum EPO level was unavailable. The difference between baseline (16.8 g/dL) and pathologic Hb levels was less than 2 g/dL. He had been diagnosed as having ET and received hydroxyurea and antithrombotic therapy. At the time of publication, patients 1 and 2 have been stable for two

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years and one and a half years, respectively. Fig. 1 shows photomicrographs of BM with histomorphology typical of a patient with ET and a patient with masked PV.

Table 1. Comparison between the 2008 WHO diagnostic criteria and the 2014 proposed revision for polycythemia vera

2008*	2014†
Major criteria	**Major criteria**
1. Hb	1. Hb
> 18.5 g/dL (men)	> 16.5 g/dL (men)
> 16.5 g/dL (women)	> 16 g/dL (women)
or other evidence of increased red cell volume‡	or Hct
	> 49% (men)
	> 48% (women)
2. Presence of *JAK2* V617F or *JAK2* exon 12 mutation	2. BM trilineage myeloproliferation with pleomorphic megakaryocytes
	3. Presence of *JAK2* mutation
Minor criteria	**Minor criteria**
1. BM trilineage myeloproliferation	1. Subnormal serum erythropoietin level
2. Subnormal serum erythropoietin level	
3. Endogenous erythroid colony growth	

*Diagnosis of polycythemia vera requires meeting either both major criteria and one minor criterion or the first major criterion and two minor criteria; †Diagnosis of polycythemia vera requires meeting either all three major criteria or the first two major criteria and one minor criterion; ‡Hb or Hct >99th percentile of method-specific reference range for age, sex, and altitude of residence, or Hb >17 g/dL in men and >15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from an individual's baseline level that cannot be attributed to correction of iron deficiency, or elevated red cell mass of >25% above mean normal predicted level. Abbreviation: BM, bone marrow.

There are a few notable differences between the WHO 2008 criteria and the proposed 2014 criteria (see Table 1). First and most noteworthy change is a lower threshold level for Hb. Accurate diagnosis is critical because compared with patients with overt PV, those with masked PV have significantly higher rates of progression to myelofibrosis and acute leukemia and worse survival [5, 6]. Second, Hct is recommended in addition to Hb for estimating red cell mass. A recent comparison between WHO criteria based on Hb levels and the revised British Committee for Standards in Haematology (BCSH) criteria based predominantly on Hct levels found that the BCSH criteria identified more patients with overt PV, which suggests that Hct may be more reliable than Hb as an indicator of increased red cell mass [7]. Third, the change to a lower threshold Hb level was reinforced by the addition of BM histomorphology to the major criteria. Because BM biopsy is an invasive procedure, clinicians have tended to diagnose PV with the criteria of elevated Hb level, the presence of *JAK2* mutation, and subnormal serum EPO level. However, a prospective study found that approximately 20% of PV patients had normal EPO levels and that BM evaluation is very valuable for the distinction of PV from ET [8].

The simplified and clarified proposed 2014 WHO criteria can facilitate the diagnosis of masked PV. Using the revised criteria, we were able to identify two patients with masked PV who had been diagnosed as having ET according to the 2008 WHO criteria. In conclusion, the 2014 criteria for *BCR-ABL1*-negative MPN ensure the straightforward identification of masked PV.
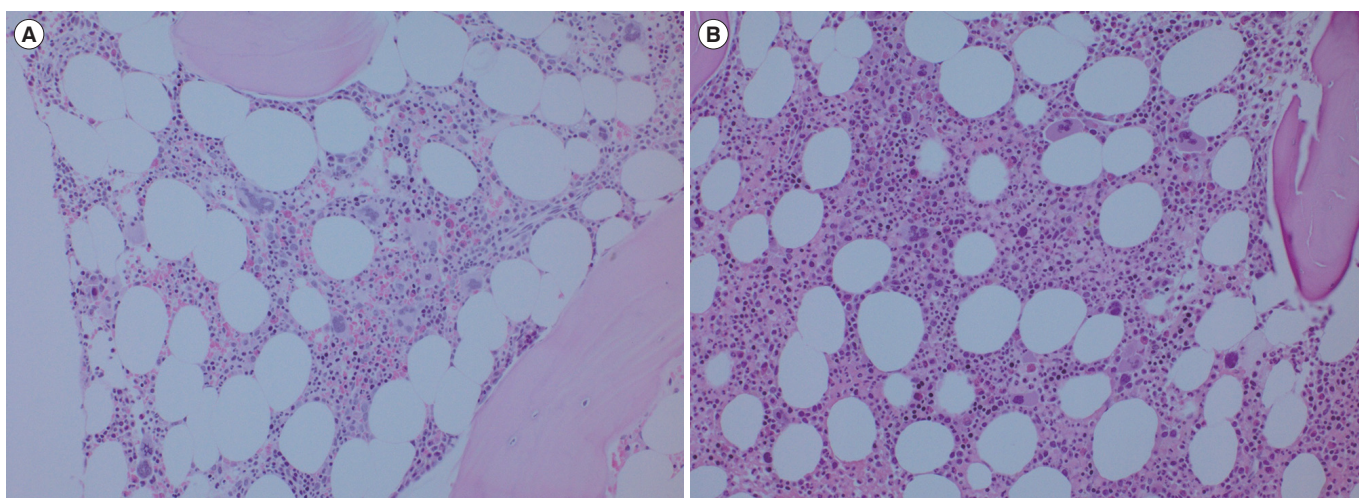
Fig. 1. Bone marrow histomorphology of essential thrombocythemia (ET) and masked polycythemia vera (PV). (A) Bone marrow morphology of ET shows normocellular marrow with an increased number of large and mature megakaryocytes. Note the hyperlobulated megakaryocytes without significant pleomorphism (bone marrow biopsy, hematoxylin and eosin [H&E] stain, ×200). (B) Bone marrow morphology of masked PV (patient 1) shows a trilineage proliferation. Note the higher cellularity compared with that in (A) and an increased number of megakaryocytes displaying cytologic pleomorphism with mild atypia (bone marrow biopsy, H&E stain, ×200).

Authors' Disclosures of Potential Conflicts of Interest

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

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