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ORIGINAL ARTICLE

Impact of World Health Organization (WHO) Revised Criteria-2016 on the Diagnosis of Polycythemia Vera

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Abstract The diagnosis of polycythemia vera (PV) requires the integration of clinical and laboratory findings, bone marrow morphologic features, and JAK2 analysis. JAK2V617F (exon 14) mutation is found in 95% of PV cases. In PV, addition of characteristic bone marrow morphology as one of three major diagnostic criteria allowed reduced hemoglobin/hematocrit threshold for diagnosis to 16.5 g/dL/49% in men and 16 g/dL/48% in women. JAK2 mutation is still the third major diagnostic criterion in PV. Low serum erythropoietin level is now considered as minor criterion in PV and is used to detect cases, which are negative for JAK2 mutation. In this retrospective study, cases diagnosed as PV from January 2013 to December 2015 were reclassified using WHO 2016 criteria. Their clinical and laboratory parameters along with treatment and outcome were studied. Out of 26 patients of previously diagnosed PV, either definitively or provisionally, twenty-one were found to comply with the new 2016 revision of the WHO Criteria. Median age was 55.5 years, with a male preponderance. The median values of hemoglobin, hematocrit and platelets were 17.5 gm/dL, 56.7% and 493 $\times$ 10^9/L, respectively. JAK2V617F was mutated in 17 cases. Bone marrow showed hypercellularity, panmyelosis and marked megakaryocyte dyspoiesis in all patients. All patients had normal oxygen saturation, confirming the primary nature of the disease. Our study, first of its kind in India, underscores the importance of the 2016 revision of the WHO document in detecting cases of masked PV.

Keywords Polycythemia vera · JAK2V617F mutation · World Health Organization revised criteria 2016 · Serum erythropoietin · Abnormal megakaryopoiesis

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Introduction

The World Health Organization (WHO) revised the diagnostic criteria for Breakpoint Cluster Region Abelson (BCR ABL) negative myeloproliferative neoplasm (MPN) in 2016 [1]. This umbrella term encompasses Polycythemia vera (PV), Essential Thrombocythemia (ET), Primary Myelofibrosis (PMF) and MPN-Unclassifiable (MPN-U). The reasons for revision of diagnostic criteria for PV were to recognize the increasingly significant role of bone marrow (BM) morphology in PV and to prevent its underreporting by including hematocrit along with hemoglobin concentration at lower thresholds. The revision also recognized the need to consider mutations other than Janus kinase (JAK2V617F) and myeloproliferative leukemia

virus oncogene (MPL) in the diagnosis of MPN. WHO criteria 2008 suggested the use of hemoglobin (Hb) threshold of more than 18.5 g/dL in males and 16.5 g/dL in females [2] and was used as a surrogate marker for increased red cell mass (RCM). This resulted in significant (46%) false negatives [3]. Thus, a large number of patients with highly suspected PV did not fulfill the 2008 WHO criteria mainly due to relatively highly set Hb levels; and these were designated as MPN-Unclassifiable (MPN-U) [2]. A comparison of both the sets of criteria is given in Table 1.

In this study, we have reclassified the cases, which were diagnosed as PV in the preceding 3 years of publication of WHO 2016 criteria. We have studied the clinico-hematological characteristics, treatment and follow up (wherever available); and compared the findings with cases diagnosed based on 2008 WHO criteria. To the best of our knowledge, this is the first Indian study, which has compared the impact of revised diagnostic criteria for PV.

Methods

A cross sectional retrospective case record based study was carried out from January 2013 to December 2015, at a tertiary care hospital, after appropriate approval from Institutional Ethics Committee.

A query based search was undertaken to retrieve data from laboratory information system (LIS) with search criteria 'polycythemia vera' in the archived bone marrow aspirate and/or bone marrow biopsy reports. This search yielded cases where PV was either definitively diagnosed or suggested a possibility of PV with a differential diagnosis of either ET or cellular phase of PMF pending Janus like kinase 2 (JAK2) mutation status and serum erythropoietin levels.

Study Population and Clinical Information

Patients of all age groups, and both sexes were included in the study. The demographics, clinical history, relevant medical history, smoking habits and radiological evidence of hepatosplenomegaly were obtained from the medical record archives.

Laboratory Parameters

Laboratory parameters—hemoglobin (Hb), hematocrit (Hct), red blood cell count (RBC), total leukocyte count (TLC), differential eosinophil and basophil counts, liver and renal profile, serum iron profile, % oxygen saturation (measured by pulsoxymetry), serum erythropoietin levels and JAK2V617F mutation status, were recorded as available on the LIS and case records.

Peripheral blood smear and BM slides (Wright stain) were retrieved from the laboratory archives and the morphology was reviewed. RBC morphology, number of basophils, presence or absence of blasts were recorded. Marrow cellularity, panmyelosis, megakaryocyte number and morphology (with respect to dyspoeitic forms—large, polylobated, antler horn, cloud like, dysplastic hyperchromatic and those with disintegrated or detached nuclei) were recorded. Abnormal localization (paratrabecular location) and clustering of megakaryocytes in the bone marrow

Table 1 Comparison of WHO criteria for the diagnosis of polycythemia vera: 2008 versus 2016

	WHO 2008 criteria[a] [2]	WHO 2016 criteria[b] [1]
Major criteria	1. Hb > 18.5 g/dL (men) > 16.5 g/dL (women) or	1. Hemoglobin > 16.5 g/dL in men; > 16.0 g/dL in women or Hematocrit > 49% in men; > 48% in women or increased red cell mass (> 25% above mean normal predicted value)
	2. Presence of JAK2V617F or JAK2 exon 12 mutation	2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
		3. Presence of JAK2V617F or JAK2 exon 12 mutation
Minor criteria	1. Bone marrow trilineage myeloproliferation	1. Subnormal serum erythropoietin level
	2. Subnormal serum erythropoietin level	
	3. Endogenous erythroid colonies (EEC) growth	

PV polycythemia vera, *JAK2* Janus like kinase 2, *WHO* World Health Organization

[a]PV diagnosis required meeting either both major criteria and one minor criterion or the first major criterion together with two minor criteria

[b]Diagnosis of PV requires meeting either all three major criteria, or the first two major criteria and the minor criterion

Table 2 Grading of myelofibrosis. Modified from WHO 2016 [2]

MF-0	Scattered linear reticulin without intersections corresponding to normal BM
MF-1	Loose network of reticulin with many intersections, particularly around blood vessels
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis

WHO World Health Organization

biopsy, number and morphology of cells in the erythroid and myeloid series, bone marrow eosinophilia and bone marrow iron stores (Perl's Prussian blue stain) were also studied. Grade of reticulin fibrosis (reticulin stain) of the marrow was determined using the criteria provided in the 2016 WHO system (Table 2).

Classification

The cases were reclassified as PV, based on the 2008 and 2016 WHO criteria (Table 1). In cases where there was only partial compliance with the diagnostic criteria and definitive diagnosis was not possible, a diagnosis of 'suggestive of PV' was given. If the morphological features were not definitive (lack of panmyelosis) or hemoglobin/hematocrit criteria were not met, then a differential diagnosis of PV, ET and cellular phase of PMF was given pending further evaluation.

Follow Up

All the patients were followed up until June 2016 (range: 1–44 months), and the general condition, the laboratory parameters and treatment details or events, if any, were recorded.

Statistical Analysis

Descriptive statistical analysis was done using SPSS version 16 (IBM, Bengaluru, India). Median values for continuous variables and range were calculated. STROBE checklist has been followed for reporting the findings of this study.

Results

The query based search yielded 26 cases. Twenty-one cases were confirmed to be PV according WHO 2016 criteria. Two cases were reclassified as ET, one as PMF and one case was excluded due to unavailability of the bone marrow biopsy slides (which were issued to the patient on request including the block). One of the cases did not meet the diagnostic criteria and hence was excluded from the study (Table 3).

The most common presenting complaint was thrombosis (57.9%), followed by weight loss (52.6%), abdominal discomfort (52.6%) and fatigue (47.4%). Two cases had a history of chronic smoking, hence were closely followed up with oxygen saturation studies by pulsoximetry and serum erythropoietin levels to confirm the diagnosis of primary PV.

The median age of PV at diagnosis was 55.5 years (range = 35–76), with a male preponderance of 76.1% (n = 16). On clinical examination, splenomegaly was seen in 80.9% (n = 17) cases. Ultrasound details were available in all the cases, with 71.4% cases showing a spleen size of grade III. Hepatomegaly was noted in 61.9% (n = 13) cases. Laboratory and clinical data are summarized in Table 4.

On bone marrow examination, all cases (21/21) had hypercellular marrow (corrected for age) and panmyelosis. Out of 26 cases 3 cases had only increased erythropoiesis and megakaryopoiesis, two of which were later diagnosed as ET (with marked megakaryocytic dyspoiesis) and one was labelled as cellular phase of PMF. Two cases had increased myelopoiesis and megakaryopoiesis with small pockets of erythroid cells. One of them was negative for

Table 3 Differences in the number of cases in each diagnostic category based on WHO 2008 and 2016 criteria

Diagnostic category	Diagnosis based on WHO 2008 criteria (n = 26)	Diagnosis based on WHO 2016 criteria (n = 26)	% change in diagnosis
Definitive diagnosis of PV	12	21	+ 34.6
Suggestive of PV	09	04	− 19.2
Differential diagnosis of PV with ET and cellular phase of PMF	05	01	− 15.4

PV polycythemia vera, *ET* essential thrombocythemia, *PMF* primary myelofibrosis, *WHO* World Health Organization

Table 4 Clinical and laboratory parameters

Clinical features	Number (n = 21)
Median age (range) in years	55.5 (35–76)
Sex	
Male	16
Female	5
Hepatomegaly	13
Splenomegaly	17
Grade	
I	0
II	2
III	15
Laboratory parameters	**Median (range)**
Hemoglobin (g/dL)	17.5 (15.9–22.5)
Hematocrit (%)	56.7 (51.2–69.5)
Total leukocyte count (10^9/L)	17.6 (11.5–55.1)
Platelet count (10^9/L)	493 (171–762)
Eosinophils (%)	3.6 (1–7.7)
Basophils (%)	2.2 (0–11)
Oxygen saturation	95.2 (91.2–98.2)
Serum erythropoietin	1 (1.10–7.58) mU/ml (n = 13)
LAP score (number of cases)	
Reduced	5
Normal/increased	1
Not done	15
JAK2V617F	
Positive	17
Negative	3
Not done	1

LAP leucocyte alkaline phosphatase, *JAK2* Janus like kinase 2

JAK2617F mutation, but serum erythropoietin levels were not tested and slides were not available for review. This case was excluded from the study. The other case was positive for JAK2617F mutation, but had normal serum erythropoietin levels with significant megakaryocytic dyspoiesis consistent with a diagnosis of ET.

Megakaryocytes were increased in all cases (21/21, 100%) with variably sized cells. Megakaryocyte dyspoeisis was also seen in all cases (21/21, 100%), with large polylobated forms being the most common, in 20/21 (95.2%) cases. Other features included, hypolobated forms in fourteen cases (66.6%), micromegakaryocytes in seven (33.3%), antler horns in six (28.5%), cloudlike in five (23.8%) and dysplastic hyperchromatic nuclei in two cases (9.5%). Clustering and para-trabecular localization were seen in 17 (80.9%) and 18 (85.7%) cases respectively. Intrasinusoidal megakaryocytes, usually a feature suggesting myelofibrosis were seen in two (10.5%) cases. Dyspoiesis was not present in erythroid and myeloid series, thus ruling out myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN). Iron stores were absent in 14 cases, whereas five cases revealed reduced iron stores. In three cases, there were inadequate number of marrow particles to assess iron stores. Serum iron levels were reduced in these cases. In cases where bone marrow aspirate was inadequate or hemodilute for definite opinion, the morphological diagnosis was based entirely on bone marrow biopsies. Reticulin stained sections showed grade 2 fibrosis in 18/21 (85.7%) and grade three fibrosis in 2/21 (9.5%) cases.

JAK2V617F mutation was positive in 18 (85.7%) cases and three cases were negative for JAK2V617F. Exon 12 mutation of JAK2 was not tested. The three negative cases satisfied the other two major criteria and two cases had low serum erythropoietin levels, hence were classified as PV. The third case where erythropoietin was not done was included in the study as PV based on typical bone marrow findings (Table 5).

The follow up period varied from 1 to 44 months, the median being 6 months. The treatment included regular phlebotomy in 12 cases, hydroxyurea in 6 cases and aspirin in 2 cases. One patient refused treatment and was lost to follow up. Out of the 21 cases, five cases have been on regular follow up. One of the patients progressed to post PV myelofibrosis and is being treated with hydroxyurea. Another patient developed pulmonary tuberculosis, completed anti-tubercular therapy and is on regular therapeutic phlebotomy. One of the patients developed severe sepsis and had chronic alcoholic liver disease. His general condition was critical, but he refused therapy and was discharged against medical advice. Rest of the cases were lost to follow up after 24 months of therapy.

Discussion

Historically, PV has been called erythemia, splenomegalic polycythemia, Vaquez disease [4, 5] Osler disease, erythrocytosis megalosplenica, cryptogenic polycythemia and myelopathic polycythemia. PV characteristically presents with panmyelosis where erythropoiesis is predominant and is independent of erythropoietin stimulation. A somatic gain of function mutations in JAK2 results in constitutive activation of JAK/STAT, PI3K/AKT, and MAPK/ERK which in turn leads to cytokine independent, erythropoietin and/or interleukin-3 hyper-responsive growth of marrow elements [6]. Classic JAK2617F mutated PVs show prominent clusters of large, bizarre megakaryocytes, which are not seen in cases with JAK2 exon 12 mutations. However, small megakaryocytic collections with significant atypia are seen in all cases [7].

Table 5 JAK2 negative cases in our series and the rationale for classification as PV

Parameters	Case 1	Case 2	Case 3
Age in years	70	54	57
Sex	Male	Female	Male
Hemoglobin (g/dL)	17.8	17.6	18.8
Hematocrit (%)	56.1	54.2	62.9
WBC count ($\times 10^9$/L)	25	14.3	15.4
Platelet count ($\times 10^9$/L)	564	465	521
Increased bone marrow cellularity, with panmyelosis and megakaryocyte dyspoeitic forms suggestive of PV	Yes	Yes	Yes
JAK2V617F mutation	Negative	Negative	Negative
JAK2 exon 12 mutation	Not done	Not done	Not done
Serum erythropoietin (mIU/mL)	1.17	3.4	Not done
Normal range: 1.9–34 mIU/mL			
Oxygen saturation (%)	97.6	97.6	91.2[a]
Diagnosis as per WHO 2008 criteria [2]	Only 2 minor criteria are satisfied; suggestive of PV	One major and 2 minor criteria are satisfied; diagnostic of PV	One major and one minor criteria are satisfied suggestive of PV
Diagnosis as per WHO 2016 criteria [1]	Two major and one minor criteria are satisfied, diagnostic of PV	Two major and one minor criteria are satisfied, diagnostic of PV	Two major criteria are satisfied suggestive of PV
Last follow up parameters			
Hemoglobin (g/dL)	16.9	15.9	14.3
Hematocrit (%)	55	58.9	45.2
Platelet count ($\times 10^9$/L)	369	214	409

PV polycythemia vera, *JAK2* Janus like kinase 2, *WHO* World Health Organization

[a]Patient underwent respiratory system evaluation and was not found to be suffering from chronic obstructive lung disease

In our study, we found that PV is a disease of the elderly, with a median range of 55.5 years, with a range of 35–76 years and male preponderance. Clinically significant findings included thrombosis, weight loss and fatigue, with a significant palpable splenomegaly. The two patients with history of chronic smoking had normal oxygen saturation (95.4 and 97.3 respectively) and subnormal serum erythropoietin levels (3.4 and 4.2 mU/ml respectively), hence were included in the primary PV group. The median hemoglobin was 17.5 gm/dL, with a hematocrit of 56.7%. Lakey et al. [7] studied 7 cases of PV which were positive for JAK2 exon 12 mutation where the median age was 46 years, with a male preponderance (male:female = 4:3). Tefferi et al. [8] studied 63 consecutive patients of PV and reported a median age of 55 years with a wide range of 18–83 years, which is similar to our study, thus substantiating that it is mainly a disease of the elderly. Although it can occur in patients as young as 2nd decade, we did not encounter any such case.

Studies done on PV, prior to the publication of the 2016 WHO document [1], reported a mean hemoglobin lower than the WHO 2008 cut off required for the diagnosis of PV. A summary of such studies and values of the present study, with comparison of WHO 2008 [2] and WHO 2016 [1] criteria is depicted in Table 6 [7, 9, 10]. With this review if literature, it is evident that the cases diagnosed using 2008 WHO criteria, represented only the tip of the iceberg. Hence, the new revision in 2016, was much needed change to identify the masked and the clinically unapparent cases.

Increased age adjusted marrow cellularity, panmyelosis and megakaryocytic dyspoiesis was noted in all cases this study. A similar study by Ghai et al. [11], from the Indian subcontinent, who studied megakaryocyte morphology in 15 cases of Philadelphia negative MPN, with seven cases of PV, revealed similar findings of increased bone marrow cellularity in 100% of the cases. Megakaryocytes were increased in number with dyspoeitic forms like hypolobated nuclei, in contrast to polylobated in our series, and few with cloud like nuclei. Clustering of megakaryocytes was seen in 6 out of 7 cases (85.7%), similar to this study. These findings confirm previously described megakaryocytic morphology [7, 12, 13]. Although WHO 2016 revision relies heavily on morphologic findings for the diagnosis of PV, evidence of abnormal megakaryocytes alone cannot definitively diagnose PV as the spectrum of

Table 6 Values and clinical data comparing contemporary studies, and the WHO 2008 versus WHO 2016 criteria for PV

Variables	Studies			
	Present study: n = 21	Lakey et al. [7] n = 7	Kyohei et al. [9] n = 38	Iurlo et al. [10] n = 13
Age (median)	55.5	46	55	61
Male gender	73.7%	57.1%	77.3%	43.7%
WBC count ($\times 10^9$/L)	17.6	9.8	16.2	8.2
Hemoglobin (g/dL)	17.5	19.5	16.7	14.3
Hematocrit (%)	56.7	–	52.4	42.5
Platelet count ($\times 10^9$/L)	493	292	648	577
EPO, mIU/mL	1	2.5	8.7	4.00
Splenomegaly	88.2%	42.8%	70%	43.7%
Thrombotic events	57.9%	–	40.9%	–
Smoking	10.5%	–	37.5%	–
JAK2V617F	84.2%	All cases had exon 12 mutation	90.9%	71.8%
WHO 2008 criteria [2]	Not met in 42% cases	Not met	Not met	Not met
WHO 2016 criteria [1]	Met for PV	Met for PV	Met for PV	Met for PV

WBC white blood cells, *EPO* erythropoietin, *JAK2* Janus like kinase, *WHO* World Health Organization, *PV* polycythemia vera

abnormal megakaryocytes is shared between Philadelphia negative CMPN [14]. Indeed, the current study, even though small in its size, demonstrates this fact (Table 3).

Lowered threshold of hemoglobin percentage, inclusion of hematocrit and bone marrow morphology as major criteria for PV diagnosis in WHO 2016 revision has led to increased definitive diagnosis by 36% in this study. Our results are similar to results of Misawa et al. from Japan [9].

Three cases in our series were negative for JAK2V617F mutation. One of these cases met the other two major criteria and the minor criterion according to WHO 2008 criteria. Two cases met the required criteria for PV diagnosis as per WHO 2016 revision. The patient who was not tested for serum erythropoietin, but classified as suggestive of PV as per WHO 2016, also responded well to therapeutic phlebotomy and low dose aspirin at the end of 40 months of follow-up.

According to the WHO classification [1], MPN-U should be used for cases with clinical, morphologic and molecular features of MPN, but failing to meet the diagnostic criteria of a specific entity or for cases presenting with overlapping features. The diagnosis of MPN-U is considered when a patient is in the initial stages of MPN where typical findings are yet to be developed. In advanced stages of MPN, presence of marked myelofibrosis and/or osteosclerosis or transformation to a more aggressive stage may mask the primary disorder-associated histologic features leading to a diagnosis of MPN-U. This may also occur in patients with coexisting neoplastic or inflammatory disorder, which obscure the MPN, related morphologic features. Prior to the 2016 revision of the WHO document, many cases of PV, ET and MF were classified as MPN-U, as they failed to meet the set criteria; hence appropriate treatment was not rendered [15, 16]. It was previously debated that cases of masked PV may be misclassified as ET leading to erroneous management. This can be avoided by testing for JAK2 mutation status, bone marrow morphology and low serum erythropoietin levels despite of lower hemoglobin/hematocrit thresholds in some cases [17]. Subsequent to the 2016 publication, many cases may now be categorized into specific types of MPN, which has lowered the number of suboptimal treatment to early/masked PV.

Conclusion

This study highlights the clinical, laboratory and bone marrow morphology of PV and importance of the WHO 2016 revision in the definitive diagnosis of PV. Although bone marrow morphology has now been included in the major criteria, dyspoiesis alone (particularly in megakaryocytic lineage) can be used for diagnosis of PV. Since, the morphologic abnormalities are shared between other Philadelphia negative CMPN, JAK2 mutation status and serum erythropoietin levels must be tested before arriving at a diagnosis of PV.

Author's Contribution SN: reviewed slides, wrote the manuscript. SL: involved in initial diagnosis, jointly prepared manuscript and critically reviewed the manuscript and is the corresponding author, also reviewed data of all patients from laboratory archives and verified the accuracy of the data. ST: collected data from patient records. SB, RK: faculty involved in initial diagnosis. CM: mentor guide for the project, reviewed slides and manuscript.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Standards The study was reviewed and approved by institutional committee at Kasturba Medical College, Manipal. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

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