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Diagnostic Challenges of Polycythemia Vera in Low- or Middle-Income Countries: Addressing the Diagnostic Gap

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INTRODUCTION

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm characterized by clonal proliferation of hematopoietic stem cells. Accurate diagnosis is crucial for appropriate management and for distinguishing PV from other causes of erythrocytosis. Limited access to key diagnostic procedures—such as Janus kinase 2 (*JAK2*) V617F mutation or *JAK2* exon 12 mutation analysis and erythropoietin (EPO) level assessment—poses significant challenges in low- or middle-income countries (LMICs).

AIM

- To explore the diagnostic landscape of PV[1] in LMICs, with a focus on the limitations associated with *JAK2* V617F or *JAK2* exon 12 mutation analysis and EPO level measurement
- To identify the diagnostic gap and its implications for PV patients in LMICs.

RESULTS

Epidemiologic data from PV patients in Armenia (2018–2020) revealed low utilization rates of critical diagnostic procedures. A total of 80 patients were diagnosed over the course of 3 years; their diagnoses were solely based on histologic analysis of bone marrow. Only 22% of patients underwent JAK2 V617F or JAK2 exon 12 mutation analysis, while 11% had EPO level measurement. These findings indicate a substantial diagnostic gap during the study period, highlighting the challenges faced in LMICs.

The shortage of availability of JAK2 V617F or JAK2 exon 12 mutation analysis and EPO level measurement in LMICs is due to financial reasons, as the majority of expenses are out of pocket for patients. Limited availability of EPO measurement exacerbates diagnostic difficulties, as levels play a crucial role in differentiating PV from secondary erythrocytosis and misdiagnosis may result in unnecessary treatments and inflated healthcare costs. Moreover, JAK2 and EPO testing could help to avoid trephine biopsy in certain patients.

1

PV

Major criteria
- Elevated Hb concentration haematocrit or increased RBC mass[†]
- *JAK2*^{V617F} or *JAK2* exon 12 mutation
- BM biopsy showing age-adjusted hypercellularity with trilineage proliferation, including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia

Minor criterion
- Subnormal serum erythropoietin level

Diagnosis
The diagnosis of PV requires either all 3 major criteria or the first 2 major criteria plus the minor criterion

Post-PV MF

Required criteria
- Previous diagnosis of PV
- BM fibrosis Grade 2/3

Additional criteria
- Anemia or loss of requirement of either phlebotomy or cytoreductive treatment for erythrocytosis
- Leukoerythroblastosis
- Increase in palpable splenomegaly of >5 cm from baseline or development of a newly palpable splenomegaly
- Development of any 2 (or all 3) of the following constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Diagnosis
The diagnosis of post-PV MF is established by all required criteria and ≥2 additional criteria

ET

Major criteria
- Platelet count ≥450 × 10^9/L
- BM biopsy showing proliferation of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters[‡]; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant BM fibrosis
- Diagnostic criteria for *BCR::ABL1*-positive CML, PV, PMF, or other myeloid neoplasms are not met
- *JAK2*, *CALR*, or *MPL* mutation

Minor criterion
- Clonal marker or absence of evidence of reactive thrombocytosis

Diagnosis
The diagnosis of ET requires either all major criteria or the first 3 major criteria plus the minor criterion

Post-ET MF

Required criteria
- Previous diagnosis of ET
- BM fibrosis Grade 2/3

Additional criteria
- Anemia and a >2 g/dL decrease from baseline Hb concentration
- Leukoerythroblastosis
- Increase in palpable splenomegaly of >5 cm from baseline or development of a newly palpable splenomegaly
- Elevated LDH level
- Development of any 2 (or all 3) of the following constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Diagnosis
The diagnosis of post-ET MF is established by both required criteria and ≥2 additional criteria

PMF, early/prefibrotic stage

Major criteria
- BM biopsy showing megakaryocytic proliferation and atypia, BM fibrosis Grade <2, increased age-adjusted BM cellularity, granulocytic proliferation, and (often) decreased erythropoiesis
- *JAK2*, *CALR*, or *MPL* mutation or presence of another clonal marker or absence of reactive bone marrow reticulin fibrosis
- Diagnostic criteria for *BCR-ABL1*-positive CML, PV, ET, MDS, or other myeloid neoplasms are not met

Minor criteria
- Anemia not attributed to a comorbid condition
- Leukocytosis ≥11 × 10^9/L
- Palpable splenomegaly
- LDH level above the reference range

Diagnosis
The diagnosis of pre-PMF requires all 3 major criteria and ≥1 minor criterion

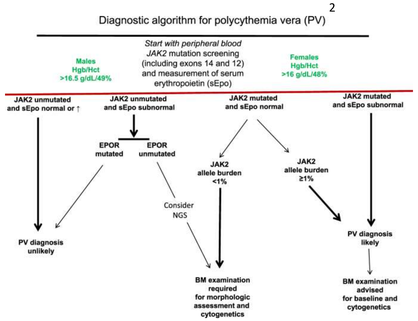
PMF, fibrotic stage

Major criteria
- BM biopsy showing megakaryocytic proliferation and atypia[§], accompanied by reticulin and/or collagen fibrosis grades 2/3
- *JAK2*, *CALR*, or *MPL* mutation or presence of another clonal marker or absence of reactive MF
- Diagnostic criteria for ET, PV, *BCR-ABL1*-positive CML, MDS, or other myeloid neoplasms are not met

Minor criteria
- Anemia not attributed to a comorbid condition
- Leukocytosis ≥11 × 10^9/L
- Palpable splenomegaly
- LDH level above the above the reference range
- Leukoerythroblastosis

Diagnosis
The diagnosis of overt PMF requires all 3 major criteria and ≥1 minor criterion confirmed in 2 consecutive determinations.

2



CONCLUSIONS

This study highlights the limitations in accessing *JAK2* V617F or *JAK2* exon 12 mutation analysis and EPO measurement in LMICs, leading to a diagnostic gap in PV. Addressing these challenges is essential for ensuring accurate PV diagnoses and improved patient outcomes in LMICs.

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