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Serum erythropoietin concentration as a diagnostic tool for polycythemia vera

Polycythemia vera (PV) is a chronic myeloproliferative disorder (CMD) with an incidence of about 10 cases per million population per year. Although its clinical course is indolent, PV has an impact on survival, the life expectancy of these patients (especially if younger than 50 years) being shorter than that of general population.[1,2]

Table 1. WHO criteria for polycythemia vera (PV)[5].

A criteria
A1. Elevated red blood cell mass (>25% more than mean normal predicted value) or Hb >18.5 g/dL in men, >16.5 g/dL in women*
A2. No cause of secondary erythrocytosis, including: absence of familial erythrocytosis; no elevation of erythropoietin (Epo) due to: hypoxia (arterial pO_2 ≤92%), high oxygen affinity hemoglobin, truncated Epo receptor, inappropriate Epo production by tumor
A3. Splenomegaly
A4. Clonal genetic abnormality other than Ph-chromosome or *BCR/ABL* fusion gene in marrow cells
A5. Endogenous erythroid colony formation *in vitro*.
B criteria
B1. Thrombocytosis >400×10^9/L
B2. WBC >12×10^9/L
B3. Bone marrow biopsy showing panmyelosis with prominent erythroid and megakaryocytic proliferation
B4. Low serum erythropoietin levels
Diagnostic use of A and B criteria
Polycythemia vera can be diagnosed when: • A1 + A2 and any other category A criterion is present. • A1 + A2 and any two of category B criteria are present.

**Or >99th percentile of method-specific reference range for age, sex and altitude of residence.*

Unlike chronic myeloid leukemia, PV lacks a molecular marker so far. In the last few years, there has been considerable interest in the overexpression of neutrophil *PRV-1* mRNA as a specific molecular marker of PV. *PRV-1* and *NB1* are alleles of the polymorphic gene *CD177*, which belongs to the Ly-6/uPAR superfamily, and their coding regions differ at only 4 nucleotides. We have recently shown that an elevated neutrophil *CD177* mRNA level is not a specific marker for the diagnosis of either PV or CMD.[3] From a clinical viewpoint, neutrophil *CD177* mRNA overexpression is rather a marker of abnormal neutrophil production and/or release in patients with CMD. Acquired uniparental disomy resulting in loss of heterozygosity of chromosome 9p may represent the most frequent chromosomal aberration in PV, but is found in only one third of patients.[4]

The diagnosis of PV is still based on combinations of clinical and laboratory parameters: Table 1 reports the WHO criteria.[5] Serum erythropoietin is considered a B category criterion, i.e., a minor criterion. However, the role of serum erythropoietin appears to be equivocal in this classification, since criterion A2 includes: *no elevation of erythropoietin (Epo) due to hypoxia (arterial pO_2 ≤92%), high oxygen affinity hemoglobin, truncated Epo receptor or inappropriate Epo production by tumor.* While arterial pO_2 can be easily assessed, the only simple way of recognizing increased erythropoietin pro-

Table 2. Pathophysiological classification of erythrocytosis.

Condition	*Epo production*
Absolute erythrocytosis (increased red cell mass)	
Genetic disorders	
Primary familiar congenital polycythemia (mutated Epo receptor gene)	Normal to low
Chuvash polycythemia (mutations in the *VHL* gene)	Increased
Primary marrow disorders	
Polycythemia vera	Normal to low
Secondary conditions with appropriately increased Epo production	Increased
Decreased oxygen loading (high altitude, pulmonary disease, congenital heart disease, sleep-apnea syndrome, carboxyhemoglobin)	Increased
Decreased oxygen unloading (high affinity hemoglobin, bisphosphoglycerate deficiency)	Increased
Secondary conditions with inappropriately increased Epo production	
Localized tissue hypoxia (renal artery stenosis, polycystic kidney)	Increased
Post-transplant erythrocytosis (kidney transplantation)	Increased
Acute hepatitis	Increased
Epo-producing tumors (Wilm's tumor, renal carcinoma, cerebellar hemangioblastoma, hepatoma)	Increased
Relative erythrocytosis (normal red cell mass)	
Marginal erythrocytosis (Hb >95th percentile)	Normal
Stress erythrocytosis (Gaisböck syndrome)	Normal
Fluid loss	Normal

duction associated with the remaining disorders is to assay serum erythropoietin itself (*en passant*, polycythemia due to truncated Epo receptor is associated with normal Epo production and more efficient signal transduction). Thus, serum erythropoietin concentration appears to have a dual role within the WHO criteria for PV, behaving as both A2 and B4 criteria.

Pathophysiology is important not only for understanding the pathogenesis of hematologic disorders but also for diagnosing them. Table 2 reports the main conditions associated with erythrocytosis and the serum erythropoietin levels found in these conditions. A quick examination of Table 2 clearly shows the fundamental importance of serum erythropoietin for the differential diagnosis of erythrocytosis and for a diagnosis of polycythemia vera. In this issue of Haematologica, Mossuz and co-workers[6] report the results of a multicenter study performed by a collaborative group of French hematologists who have been working for years on new diagnostic approaches to PV. In this work, their objective was to statistically validate the utility of serum Epo for diagnosis of PV by using a standardized commercial ELISA kit that gives reliable, reproducible results whatever the Epo level in serum. Their results clearly show that serum Epo level provides a reliable and accurate biological criterion that by itself can allow the definitive diagnosis of PV in 2/3 of patients. This indicates that the serum Epo assay should become a first-intention test in the work-up of absolute erythrocytosis and a major diagnostic criterion for polycythemia vera.

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