



COMMENTARY

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## Polycythemia Vera: The Development of Balance between Molecular Routes and Blood Cells

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### About the Study

Polycythemia Vera (PV) is a rare but significant disorder characterized by the overproduction of red blood cells (erythrocytosis), white blood cells, and platelets. This condition falls under the category of Myelo Proliferative Neoplasms (MPNs), which involve abnormal growth and function of bone marrow cells. PV often leads to an increase in blood viscosity, which can result in serious complications such as thrombosis and hemorrhage. The exact cause of PV remains unknown, although it is believed to involve acquired mutations in hematopoietic stem cells. The most common mutation associated with PV is a gain-of-function mutation in the *JAK2* gene, specifically *JAK2* V617F, which leads to constitutive activation of the Janus Kinase 2 (*JAK2*) signalling pathway. Other mutations, such as in the genes for thrombopoietin receptor and calreticulin are also observed in a subset of PV patients, further contributing to the dysregulated proliferation of blood cells.

The pathogenesis of PV involves dysregulated signalling pathways that promote abnormal growth and survival of hematopoietic cells. The *JAK2* V617F mutation leads to the activation of downstream signalling pathways, including the Signal Transducer and Activator of Transcription (STAT) pathway. Constitutive activation of *JAK2* results in increased sensitivity to cytokines such as erythropoietin, thrombopoietin, and granulocyte colony-stimulating factor, leading to uncontrolled proliferation of erythroid, megakaryocytic, and myeloid progenitor cells. The increased generation of mature blood cells, especially red blood cells, as a result of PV's larger number of hematopoietic stem cells causes erythrocytosis. The increased quantity of red blood cells makes the blood more viscous, which affects microcirculation and puts patients at risk for

thrombotic attacks. Additionally, increased platelet and leukocyte counts contribute to the prothrombotic state observed in PV patients.

The clinical manifestations of PV are diverse and often nonspecific, making diagnosis challenging. Common symptoms include headache, dizziness, fatigue, pruritus and erythromelalgia (burning pain and redness in the extremities). Certain patients can experience thrombotic events, such as myocardial infarction, stroke, or deep vein thrombosis, whereas other patients may undergo periods of bleeding as a result of platelet dysfunction or acquired von Willebrand disease. Untreated or poorly controlled PV can lead to serious complications, including thrombosis, hemorrhage, and transformation to myelofibrosis or acute leukemia. Thrombotic events, such as stroke or myocardial infarction, are a leading cause of morbidity and mortality in PV patients. The hyper viscosity of the blood increases the risk of thrombosis, particularly in the cerebral and coronary arteries.

Reduced levels of high-molecular-weight von Willebrand factor compounds are a hallmark of acquired von Willebrand disease, which can lead to hemorrhagic consequences. Additionally, patients with PV are at increased risk of developing secondary malignancies, such as solid tumors or hematologic malignancies, possibly due to the effects of chronic inflammation and the use of cytotoxic therapies.

A combination of clinical, laboratory, and histopathologic findings are used to diagnose PV. A Complete Blood Count (CBC) with differential is usually part of the first evaluation, and it frequently shows erythrocytosis, leukocytosis, and thrombocytosis. Increased red cell mass may be seen in peripheral blood scans, along with other morphologic abnormalities such as basophilia and enlarged red

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cell size. To evaluate cellularity, morphology, and the existence of fibrosis or myelofibrosis, bone marrow biopsies are frequently carried out. The detection of the *JAK2* V617F mutation or other mutations associated with PV is essential for confirming the diagnosis. Molecular testing can be performed using Polymerase Chain Reaction (PCR) or allele-specific PCR techniques to detect specific mutations in peripheral blood or bone marrow samples.

The management of PV aims to reduce the risk of thrombotic complications, control symptoms, and improve overall survival. Phlebotomy is the primary treatment modality for reducing red blood cell mass

and hematocrit levels. Cytoreductive therapy may be considered for patients at high risk of thrombosis, particularly those with a history of thrombotic events or cardiovascular risk factors. Hydroxyurea, interferon-alpha, and ruxolitinib are commonly used cytoreductive agents in PV. In addition to pharmacologic therapy, lifestyle modifications such as smoking cessation, maintaining hydration, and avoiding extreme temperatures can help reduce the risk of thrombotic events. Regular monitoring of blood counts, symptom assessment, and screening for complications are essential components of long-term management.