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Perspective

Polycythemia Vera and Its Clinical Complexities: From Diagnosis to Advanced Management

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DESCRIPTION

Polycythemia Vera (PV), a chronic myeloproliferative neoplasm characterized by increased erythrocyte mass and clonal proliferation within the bone marrow, presents a unique spectrum of clinical, pathological, and therapeutic challenges that continue to evolve alongside advances in molecular hematology. Driven predominantly by acquired somatic mutations-most notably Janus Kinase 2 valine (V) at position 617 is replaced by phenylalanine (F)(JAK2 V617F), present in the overwhelming majority of cases, and less commonly JAK2 exon-12 variants-PV reflects a disruption of normal hematopoietic regulation in which erythroid lineage expansion occurs independently of physiological feedback control.

This dysregulated erythropoiesis not only results in elevated hemoglobin and hematocrit values but also fosters microcirculatory disturbances, hyperviscosity, and thrombotic vulnerability. Clinically, PV is insidious in onset; early symptoms such as fatigue, headache, pruritus, and dizziness are nonspecific, often delaying diagnosis until laboratory abnormalities or major vascular events occur. Splenomegaly, pruritus exacerbated by water exposure, erythromelalgia, and progressive leukocytosis or thrombocytosis further complicate the phenotype, underscoring the disease's systemic footprint and chronic inflammatory signature.

The diagnosis of PV requires an integrated assessment combining clinical suspicion, hematologic measurement, molecular detection, and histopathologic confirmation. The 2016 World Health Organization (WHO) diagnostic criteria emphasize sustained elevated hemoglobin or hematocrit, bone marrow hypercellularity with trilineage growth, and the presence of a JAK2 mutation, with reduced serum erythropoietin serving as a supportive minor criterion. Yet clinical complexity emerges when PV overlaps phenotypically with secondary erythrocytosis, masked Polycythemia Vera (PV), or essential thrombocythemia with an erythrocytosis-dominant profile. In these cases, bone marrow morphology and genetic profiling are indispensable.

Importantly, early recognition is critical because morbidity in PV is strongly associated with macrovascular and microvascular thrombotic complications, including stroke, myocardial infarction, portal vein thrombosis, and pulmonary embolism. These complications are not merely consequences of elevated blood viscosity but also reflect endothelial activation, platelet–leukocyte interactions, chronic cytokine drive, and heightened coagulability. Paradoxically, disease progression also carries risks of hemorrhage, due in part to acquired von Willebrand factor abnormalities in the setting of extreme thrombocytosis.

Management approaches in PV have transitioned from purely hematocrit-focused strategies to multidimensional care models incorporating molecular, inflammatory, and thrombo-preventive pathways. Traditional therapy has centered around phlebotomy to maintain hematocrit below 45%, low-dose aspirin to reduce thrombotic risk, and cytoreduction-most commonly with hydroxyurea—in high-risk individuals (age >60 or prior thrombosis). However, the therapeutic landscape has shifted dramatically with greater understanding of disease biology. Ruxolitinib, the first Janus Kinase (JAK) inhibitor approved for PV refractory to hydroxyurea, has achieved notable success in controlling hematocrit, reducing splenomegaly, alleviating pruritus, and attenuating systemic inflammation. Interferon-based therapies, particularly pegylated interferons and next-generation targeted interferon molecules, have shown promise in inducing deeper molecular remissions, including reduction in *JAK2* allele burden.

For younger patients, or those seeking disease modification rather than cytoreduction alone, interferon has increasingly emerged as a frontline option. Additionally, research into metabolic vulnerabilities of malignant clones, immunologic modulation, and precision targeting of epigenetic regulators continues to expand the conceptual framework of PV treatment.

Long-term disease behavior introduces further complexity. Over years to decades, PV may transform into post-polycythemia myelofibrosis or, more rarely, acute myeloid leukemia, reflecting clonal evolution driven by secondary mutations in Tumor Protein 53 (TP53), Ten-Eleven Translocation 2(TET2), Additional Sex Combs-Like 1(ASXL1), DNA (Cytosine-5)-Methyltransferase 3A (DNMT3A), and others. These late-phase transitions are associated with worsening anemia, progressive

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splenomegaly, bone marrow fibrosis, constitutional symptoms, treatment refractoriness, and shortened survival.

Thus, emerging clinical guidelines increasingly prioritize not only thrombosis prevention but also disease-modifying strategy, quality of life, and surveillance for early transformation. Patient-specific management now integrates genetic risk stratification, symptom burden assessment, metabolic markers, and marrow architecture. In addition, lifestyle measures-including smoking cessation, cardiovascular risk control, and physical activity-are essential adjuncts in mitigating disease impact.

CONCULSION

As molecular hematology advances, PV is shifting from a disease defined solely by erythrocyte excess to one understood through the lens of aberrant stem-cell biology, chronic inflammation, microvascular pathology, and clonal progression. Its complexity demands continuous diagnostic vigilance, nuanced therapeutic planning, and long-term monitoring. Ultimately, modern PV management strives not only to maintain safe hematologic indices, but also to delay disease evolution, minimize vascular risk, alleviate symptom burden, and restore physiological balance. The trajectory of future research, increasingly centered upon targeted therapy, gene-directed correction, and immune clonal modulation, promises a redefinition of prognostic expectations and may lay the groundwork for curative intervention in what has long been considered a chronic, progressive hematologic disorder.