Polycythemia and Thrombocytosis

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KEYWORDS

• Myeloproliferative neoplasms • Polycythemia vera • Essential thrombocytosis
• Myelofibrosis • *JAK2* mutation

KEY POINTS

- Polycythemia vera (PV) involves excess red blood cell production, whereas essential thrombocytosis (ET) involves an excess of platelets.
- The myeloproliferative neoplasms (MPNs) share underlying mutations, particularly *JAK2V617F*, seen in nearly all cases of PV and roughly half of all cases of ET and myelofibrosis.
- Although some patients present with generalized symptoms and splenomegaly, many are asymptomatic at presentation and are identified by routine laboratory testing.
- The mainstay of PV therapy is phlebotomy and low-dose aspirin, although for both PV and ET cytoreductive agents and selective JAK2 inhibitors (ruxolitinib) may also be used.
- Patients with PV and ET are at risk for both thrombotic and hemorrhagic complications, and a subset of patients progress to myelofibrosis and acute myeloid leukemia, leading to a worsened prognosis.

INTRODUCTION

Overview

Myeloproliferative neoplasms (MPNs) are a group of disorders marked by abnormal proliferation of immature and mature myeloid cells from the bone marrow. They are driven by the presence of an abnormal neoplastic stem cell clone that gives rise to excess red blood cells (RBCs), white blood cells, and/or platelets. This clone is presumed to harbor underlying genetic mutations that confer unchecked growth and proliferation.[1]

Classification

In the past, MPNs have been separated into those diseases involving the *BCR-ABL1* gene fusion (also known as the Philadelphia chromosome, a marker of chronic

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myelogenous leukemia [CML]; See Page Widick and Eric S. Winer's article, "Leukocytosis and Leukemia", in this issue) from those that do not, such as polycythemia vera (PV), essential thrombocytosis (ET), and myelofibrosis (MF).

Although PV is defined by increased erythrocyte level and ET is defined by increased platelet level, there can be a degree of clinical overlap (**Table 1**).[1]

Genetics

The clinical resemblance of MPNs has led to a long-standing suspicion that these disorders have a shared genetic basis. Since the advent of gene sequencing, several genetic mutations have been identified in both PV and ET, improving the understanding of the molecular biology of these diseases.

The most common mutation in these cases targets the protein Janus kinase 2 (JAK2), a nonreceptor tyrosine kinase. JAK2 helps mediate signals from outside the cell to drive growth and differentiation. When cytokine receptors bind to ligands (erythropoietin [Epo], thrombopoietin, or interleukins) they induce phosphorylation of JAK2, which then activates downstream signaling cascades to cause transcription of new genes (**Fig. 1**).[2]

The most frequently seen mutation is *JAK2V617F* (in exon 14), which inactivates an inhibitory domain of the protein to trigger cytokine independent growth. This mutation is seen in nearly all cases of PV, as well as more than half of all ET and MF cases (**Fig. 2**). The remaining 4% of PV cases without this classic mutation typically harbor alternative mutations in JAK2 exon 12.[2,3]

The burden of JAK2 mutations in ET and primary myelofibrosis is less than for PV, estimated at 50% to 60%, with an additional 25% attributed to calreticulin (CALR) mutations, and 5% attributed to myeloproliferative leukemia protein (MPL) mutations. The remaining 15% are termed triple negative.[1,4–6] These 3 mutations are mutually exclusive.

POLYCYTHEMIA VERA

Definition

PV is a clonal disorder of excess RBC production by the bone marrow.

Epidemiology

- Between 1 and 40 per 100,000 people
- Slight male predominance
- Median age of mid-60s at diagnosis
- Familial pattern in only rare cases[1,4,7]

Table 1
Classification of MPNs

Myeloproliferative Neoplasm (MPN)	Hallmark
Philadelphia Chromosome (*BCR-ABL1*) Positive	
CML	Excess white blood cells
Philadelphia Chromosome (BCR-ABL1) Negative	
PV	Excess RBCs
ET	Excess platelets
MF	Megakaryocyte proliferation within a fibrotic bone marrow