blood® Editorial



# Introduction to a review series on classic myeloproliferative neoplasms

In a visionary editorial of 1951, William Dameshek wrote, "it becomes more and more evident that the bone marrow cells (erythroblasts, granulocytes, megakaryocytes) often proliferate en masse or as a unit rather than as single elements."[1] He initially focused on polycythemia vera (PV), underlining that this condition was far more than a pure red blood cell proliferation, with many patients showing pancytosis (erythrocytosis, leukocytosis, and thrombocytosis) and generalized bone marrow hypercellularity. The overall conclusion of Dameshek's editorial was that PV, essential thrombocythemia (ET), and primary myelofibrosis (PMF; or agnogenic myeloid metaplasia of the spleen and liver) were closely interrelated.[1]

At my institution in Pavia, Italy, we started collecting data of well-defined populations of patients with classical myeloproliferative neoplasm (MPN) decades ago. When we published our first report about the natural history of PV and ET in the fall of 2004,[2] the state of the art in the field was, more or less, as the one depicted in Dameshek's editorial. But a few months before that, the molecular revolution had already started.

The discovery of the somatic, gain-of-function *JAK2* (V617F) mutation in MPNs was described in 4 papers published in March and April 2005.[3-6] However, at Gustave Roussy, Paris, William Vainchenker and his collaborators had already identified the *JAK2* (V617F) mutation in June 2004. Based on their previous observation that JAK2 inhibitors suppressed erythropoietin-independent colony formation in PV,[7] they sequenced the *JAK2* gene in 3 patients with PV and found that 2 of them carried the somatically acquired *JAK2* (V617F) mutation. Interestingly, the third patient, who tested negative for *JAK2* (V617F), was later found to carry a somatic mutation of *JAK2* exon 12 (William Vainchenker, written communication, 8 February 2023). The discovery of *JAK2* (V617F) opened avenues of research, and somatic mutations of *MPL* were soon detected in ET and PMF.[8-10] Patients with PV who were tested negative for *JAK2* (V617F) mutation were found to carry *JAK2* exon 12 mutations.[11,12] In 2013, 2 seminal papers described somatic mutations of *CALR*, the gene encoding calreticulin, in patients with ET or PMF, which was not associated with a *JAK2* or *MPL* alteration.[13,14] Along with bone marrow histology (Figure 1),[15] these genetic lesions now represent important criteria in the classification and diagnostic workup of classical MPNs.[16,17] Additionally, it soon became clear that many patients with MPN also carry somatic mutations other than *JAK2*, *CALR*, or *MPL in* myeloid genes.[18]

The review series articles in this issue of *Blood* describe the latest advances in our understanding of the classical MPNs:

- Damien Luque Paz, Robert Kralovics, and Radek C. Skoda, "Genetic basis and molecular profiling in myeloproliferative neoplasms"
- Joan How, Jacqueline S. Garcia, and Ann Mullally, "Biology and therapeutic targeting of molecular mechanisms in MPNs"
- Alison R. Moliterno, Hannah Kaizer, and Brandi N. Reeves, "*JAK2*$^{V617F}$ allele burden in polycythemia vera: burden of proof"
- Anna L. Godfrey, Anna C. Green, and Claire N. Harrison, "Essential thrombocythemia: challenges in clinical practice and future prospects"
- Francesco Passamonti and Barbara Mora, "Myelofibrosis"

In their analysis of the mutational landscape of the classical MPNs, Luque Paz, Kralovics, and Skoda differentiate between germ line predisposition variants, clonal mutations, MPN driver mutations, and disease progression–associated mutations. How, Garcia, and Mullally review recent data elucidating the mechanisms of disease in MPNs and focus on those with therapeutic potential. Moliterno, Kaizer, and Reeves analyze the role of *JAK2* (V617F) variant allele frequency (or mutant allele burden) in PV outcomes and conclude that lowering this parameter should be considered an important end point in clinical trials. Godfrey, Green, and Harrison provide a practical overview of the diagnosis and management of ET, with a focus on difficult patient scenarios. Passamonti and Mora discuss myelofibrosis, which includes primary myelofibrosis, post-PV, and post-ET myelofibrosis. The authors underline that modern prognostication of myelofibrosis is central to treatment plans and discuss the currently available prognostic models to predict survival. Available medical treatments include those directed toward anemia, hydroxyurea, and JAK inhibitors. So far, allogeneic stem cell transplantation remains the only potentially curative treatment for patients with myelofibrosis, which is regretfully still associated with morbidity and mortality.

I hope that these articles will help the readers of *Blood* improve their knowledge of classical MPNs.

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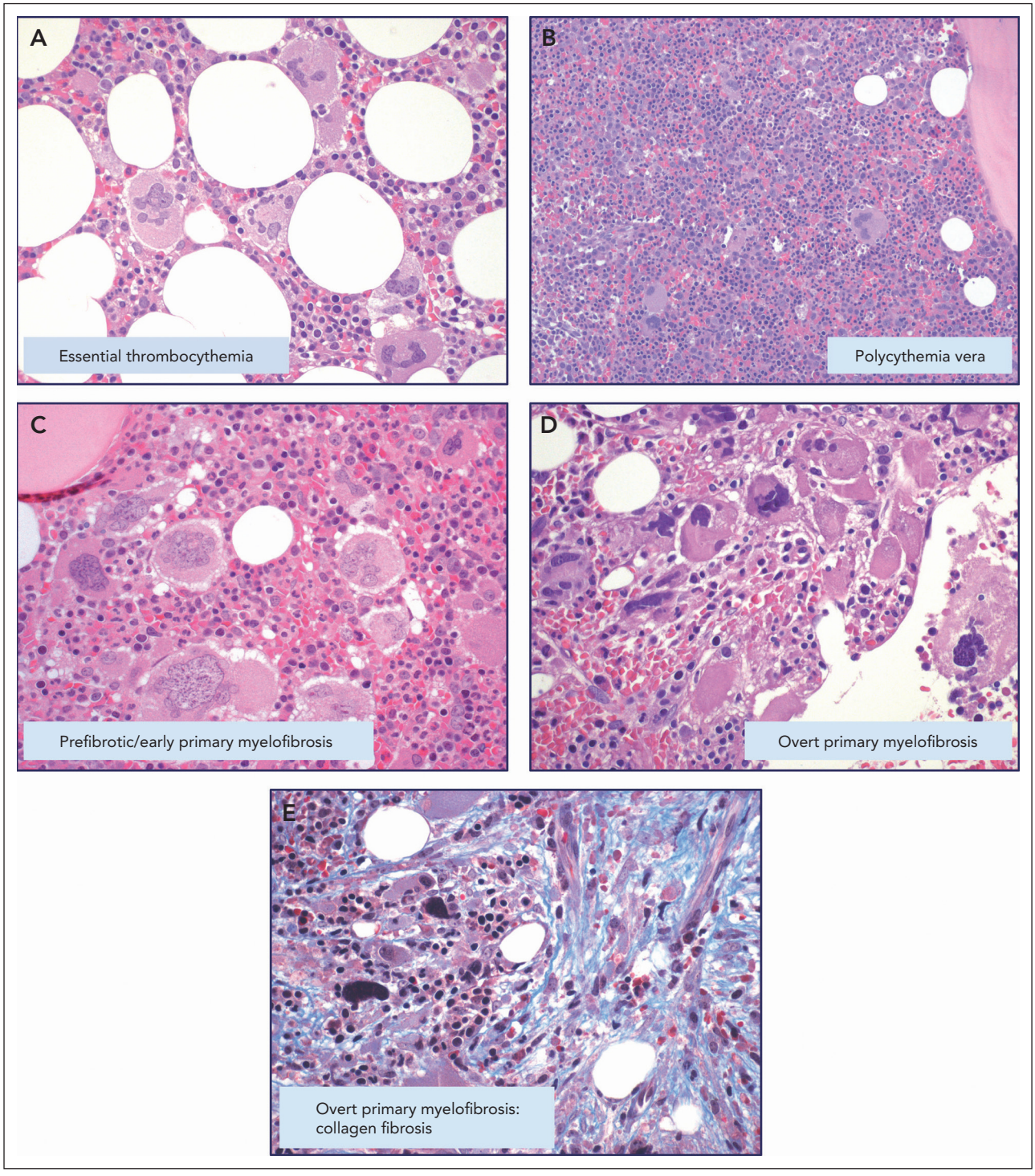


**Figure 1. Representative bone marrow biopsies from patients with MPNs.** (A) ET: normocellular marrow with the proliferation of giant megakaryocytes with hyperlobulated nuclei scattered or in loose clusters (hematoxylin and eosin [H&E]). (B) PV: hypercellular marrow with erythroid proliferation and scattered pleomorphic megakaryocytes (H&E). (C) Prefibrotic PMF: hypercellular marrow with granulocytic proliferation and large megakaryocytes with atypical bulbous nuclei (H&E). (D) Overt PMF: hypercellular marrow, proliferation of atypical megakaryocytes forming dense clusters, and dilated vessels with intraluminal hematopoiesis (H&E). (E) Overt PMF (collagen fibrosis): bands of collagen fibrosis within hematopoietic lacunae (Masson trichrome staining). Original magnifications ×40 (A,C-E) and ×20 (B). Reproduced from Rumi and Cazzola.[15]

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