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Myeloproliferative disorders

ONE HUNDRED SUSPECTED MYELOPROLIFERATIVE NEOPLASMS WITH A *JAK2* V617F VARIANT ALLELE FREQUENCY <2%: CLINICAL, GENETIC AND HISTOPATHOLOGICAL CORRELATES

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Introduction: *JAK2* V617F (*JAK2*) is the most frequent driver mutation in myeloproliferative neoplasms (MPN), but it was found in healthy individuals with clonal hematopoiesis of indeterminate potential (CHIP), though its role in CHIP remains debated (Leukemia 2021;35(9):2706-2709). We examined clinical, genetic, and morphological features in suspected MPN cases with *JAK2* VAF <2%.

Methods: We included 100 suspected MPN cases with *JAK2* VAF <2% (2010–2025). After excluding secondary causes, patients were grouped as follows: erythrocytosis (n=35), thrombocytosis (n=47), and miscellaneous (n=18; detailed in **Figure 1**). All samples and data were collected at diagnosis. *JAK2* VAF was assessed in granulocytes by dd-PCR (limit of detection 0.01%); BM biopsies were reviewed by R.S. and U.G. (Blood 2022; 140(11):1200-1228).

Results: Overall, median age was 62 years, male 64%, median *JAK2* VAF 0.22%. Median (range) leukocyte count was 7.6 x 10^9/L (5-30), hemoglobin 14.6 g/dL (9-19.5), hematocrit 43.5% (28-57), platelets 408x10^9/L (98-1450). Previous history of venous and arterial thrombosis in 10%/12%, respectively. No age differences among 3 groups (p=0.8), whereas patients with erythrocytosis were mostly male (91% vs. 42% vs. 67%, p<0.01), EPO value subnormal in only 1 case. Driver mutations other than *JAK2* were documented in 33 patients: 24 *CALR* comprising type-1 (n=17), type-2 (n=5), atypical (n=2) and 9 *MPL* (7 at p.W515 and 2 at p.S505). Of note, double driver mutated cases constituted 68% of all those with thrombocytosis. Respective median VAF for *CALR* /*MPL* mutations were 34%/21%. Considering patients with thrombocytosis, those with JAK2 only vs. double mutated were mostly ET (93% vs. 60%, p=0.03), had lower platelets (546 vs. 845x10^9 /L, p<0.01), and higher *JAK2* VAF (0.55 vs. 0.15%, p=0.04). Additional NGS mutations were reported in 24 (52%) cases, mostly, in miscellaneous group (75%, p=0.2); overall, the most represented were *ASXL1* (13%), *TET2* (7%), *SH2B3* (7%), *KIT* (7%), *DNMT3A* (7%), *NF1* (7%) mutations. 9% showed abnormal karyotypes (7 cases –Y, 1 case -22, 1 case +13), with similar distribution across the groups.
Considering patients with erythrocytosis, BM histologic features were consistent with PV in 8 cases whereas the other 27 cases showed age-adjusted normal/focally increased cellularity, regular/mildly expanded erythroid lineage consistent with a diagnosis of MPN unclassifiable (MPN-U). Among patients with thrombocytosis and miscellaneous group, diagnosis are reported in **Figure 1**.

Conclusions: This study underscores the significance of employing highly sensitive assays for the detection of *JAK2*, as well as emphasises the necessity of concurrent screening for *CALR* and *MPL* mutations in patients presenting with thrombocytosis and low *JAK2* VAF. In those with erythrocytosis, early histopathological signs of MPN can be subtle, so integrating histopathology with clinical and genetic data is essential for an appropriate diagnosis.

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