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ABSTRACT N. PO51

THROMBOCYTHEMIA ASSOCIATED WITH A NON-CANONICAL JAK2 MUTATION: A CASE REPORT.

G. Rosati, A. Pozzi, M. Padrini, S. Laurenti, G. Ferrari, R. M. Medici, C. Barale, I. Russo, A. Morotti.

Univeristy of Turin, AUO San Luigi Gonzaga, Orbassano - TO.

Background

Myeloproliferative neoplasms (MPNs) are hematologic malignancies marked by clonal myeloid proliferation in the bone marrow. Common genetic drivers include JAK2-V617F, JAK2 exon 12, MPL, and CALR mutations. However, some patients with myelofibrosis (MF) or essential thrombocythemia (ET) are "triple negative," likely due to non-canonical mutations, as seen in the following case.

Case Report

In January 2024, a 23-year-old woman was referred for thrombocytosis found during routine bloodwork. Her history included only a paracetamol allergy and a prior asymptomatic SARS-CoV-2 infection. From 2018 to 2021, platelet counts were normal, but in January 2024 they had risen to 540,000/µL. White blood cell count was mildly elevated; hemoglobin was normal. She reported no bleeding or infection history. C-reactive protein and iron studies were normal. Chest and abdominal ultrasounds showed no abnormalities. With suspicion of an MPN, molecular testing for BCR/ABL, JAK2, MPL, and CALR mutations was performed—all negative. As platelets rose to 600,000/µL, a bone marrow biopsy was done, revealing megakaryocyte hyperplasia and mild fibrosis—findings consistent with ET. Next-generation sequencing identified two mutations: CBL 1227+4C>T and JAK2 3188G>A. A diagnosis of essential thrombocythemia was confirmed, and low-dose antiplatelet therapy was started. By February 2025, the patient remained asymptomatic with stable platelet counts (540,000/µL).

Conclusions

Beyond canonical mutations, MPNs may involve somatic alterations in other genes, including those related to signal transduction (CBL, SH2B3), chromatin remodeling (TET2, ASXL1, DNMT3A, EZH2, IDH1/2), RNA splicing (SF3B1, ZRSR2), and tumor suppression (TP53). These additional mutations often have prognostic significance. In MF, for instance, CBL mutations may be linked to poorer survival post-transplant.

The CBL 1227+4C>T variant (rs201747825) is intronic and reported as "benign" in ClinVar (8 submissions). It appeared in a 2018 study as an "additional mutation" in a patient with juvenile myelomonocytic leukemia but without clinical relevance. The JAK2 3188G>A mutation (R1063H) was first described in 2005 in U.S. patients with polycythemia vera. It later appeared in compound form with JAK2 E816D in a case of erythrocytosis with megakaryocyte atypia, implicating JAK-STAT pathway dysregulation. A 2018 Belgian-Romanian study found R1063H in 14 JAK2-V617F+ patients, mostly with ET, suggesting possible inheritance. The mutation was also found in a 2019 German patient with triple-negative MF, and in a 2023 Brazilian ET patient. A 2025 dataset reported 2,042 carriers, while 2017 and 2020 studies linked it to idiopathic venous thrombosis and cryptogenic stroke. ClinVar currently classifies R1063H as benign, based on nine submissions. While both variants are individually documented, their coexistence in a triple-negative MPN patient remains rare and underreported. This case highlights the need for further investigation into non-canonical mutations and their potential roles in MPN pathogenesis, especially in the absence of common driver mutations. Their identification could inform future diagnostic and prognostic strategies in seemingly triple-negative cases.

Email: *alessandro.morotti@unito.it*

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