HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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Letter to the Editor

Monoclonal gammopathy and myeloproliferative neoplasm molecular diagnostics

Dear Editor,

The myeloproliferative neoplasms (MPNs) are a group of chronic, hematological stem cell malignancies characterized by an over-production of mature myeloid cells that manifest clinically with an increased risk of thrombotic events and a tendency to transform into acute myeloid leukemia. At the molecular level, the most frequent, somatic "driver" mutations of the MPN are those within the *JAK2, CALR* and *MPL* genes which are present in over 90% of the MPNs. These acquired mutations disrupt normal intracellular Janus kinases signal transducers and activators of transcription (JAK-STAT) signaling in hematopoietic cells. A recurring feature of MPN patients is a monoclonal gammopathy (MG),[1] present in up to 15% of patients and suggested to impact on the clinical outcome.[2] Moreover, not only can monoclonal plasma cell neoplasms, such as myeloma, co-exist with the MPN, but can also present with hematological features suggestive of an MPN, such as erythrocytosis or thrombocytosis.[3]

Because of these pathological associations, a retrospective audit was performed to determine whether screening for MPN-associated mutations is clinically indicated in the investigation of patients with an MG. Reviewing requests for MPN molecular diagnostics from January 2006 to December 2022 at a center for molecular diagnostics of hematological malignancies, a total of 270 requests were identified with MG and included in the clinical details. Patient consent was required at the referring center. Testing was performed on DNA extracted from peripheral blood ($n = 259$), or on bone marrow aspirate ($n = 11$) samples. Of these 270, thirty-two (11.9%) had additional details of either an erythrocytosis, or an elevated hemoglobin or hematocrit, and a further forty-seven (17.4%) requests had additional details of a persistent thrombocytosis. All samples were tested for *JAK2* V617F, 214, for *CALR* exon 9 mutations and 132, for both *MPL* exon 10 and *JAK2* exon 12 mutations. The MPN-associated mutations were detected in one patient (0.5%: *JAK2* V617F, $n = 1$) in the MG only group, in three patients in the MG-erythrocytosis group (9.4%: *JAK2* V617F $n = 2$, *JAK2* exon 12 $n = 1$) and in six patients in the MG-thrombocytosis group (12.8%: *JAK2* V617F $n = 5$, *CALR* exon 9 $n = 1$). The difference in MPN-associated mutation incidence rate between the MG only group (1/191 = 0.5%) and those patients with additional details suggestive of an MPN (9/79 = 11.4%) is statistically significant ($p < 0.0001$; 95% Confidence Interval −0.1591 to −0.0582) (www.medcalc.org/calc/rate_comparison.php). The single patient with MG only had a platelet count of 392×10^9/L at the time of the *JAK2* V617F-testing that had increased to 471×10^9/L within five months.

This brief audit suggests that reflexive screening for MPN-associated mutations remains of value in those patients with MG and hematological parameters suggestive of an MPN, as in normal practice, but is unwarranted in patients with an isolated MG. The presence of monoclonal immunoglobulin in such myeloid malignancies remains paradoxical: an inflammatory profile is a significant feature of many MPNs. Additionally, common to B-cell neoplasms, such as myeloma and MPN, are disruption of the JAK-STAT pathway signaling and a shared genetic susceptibility,[4,5] further investigations of which might provide insight into this pathological association.

Conflicts of interest

The author declares no conflicts of interest.

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