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EDITORIAL

Myeloproliferative Neoplasms, an Acquired Thrombophilic State: *JAK2* and Beyond

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In the current issue of IJHBT, Uyanik et al. [1] present data from 101 patients with essential thrombocythemia (ET) and polycythemia vera (PV) with reference to the development of thrombotic complications. The paper provides interesting insights into this fascinating, and clinically highly relevant aspect of the Ph-negative myeloproliferative neoplasms (MPN).

Vascular events comprise the presenting complaints in approximately 12–39 % of PV and ET patients [2]. Subsequently too, they continue to cause morbidity and mortality, especially as these patients now live longer with effective therapies [2]. Evidence-based prediction of the risk of thrombosis and preventing them is therefore a priority management goal. The International Prognostic Score of Thrombosis in ET (IPSET) introduced in 2012 combined conventional markers of thrombotic risk (age, cardiovascular risk factors, prior history of thrombosis) with *JAK2* mutation status to make this assessment more objective [3]. Since then, the search for novel markers of thrombotic risk has only intensified.

The *JAK2* mutation, if present, is a well-established risk factor for thrombosis in ET [3, 4], a finding has also confirmed in the publication by Uyanik et al. [1]. The V617F allele burden is known to be associated with acquired activated protein C resistance, low free PS and increased levels of soluble markers of endothelial and platelet activation including elevated tissue factor [5–7]. It also correlates with less conventional biomarkers of risk, including C-reactive protein, the inflammatory marker pentraxin-3 and circulating micro-particles and reticulated platelets [8–10]. Intriguingly, an inherited *JAK2* 46/1 haplotype may modulate thrombotic risk in some patients without the acquired mutation as well [11].

JAK2 mutations are however, only one cog in the complex multi-factorial wheel of MPN-related thrombogenesis. Perturbations are known of several cellular elements (both quantitative and qualitative abnormalities of red and white cells, platelets and endothelial cells), subcellular humoral mediators (coagulation pathways and their inhibitors, intercellular adhesion molecules, secondary mediators, inflammatory cytokines and their metabolites) as well as rheological aspects including shear stress and hyperviscosity [2, 5–8, 10]. The biological links between the genetic events and the ultimate macromolecular and cellular phenotypes is not always clear-cut but advances are underway.

For instance, Teofili et al. [12] demonstrated that MPN patients whose cultured endothelial cells showed clonality and/or *JAK2* V617F mutation positive were significantly more likely to thrombose and require anti-proliferative therapy. Endothelial cell numbers, whether resting or activated are increased in MPN, as are levels of endothelial activation and aggregation markers like von Willebrand factor, thrombomodulin and various selectins. Chronic endothelial dysfunction in PV may result from high shear stress of hyperviscosity as well [6, 7]. Similarly, Tan et al. [13] contended that their finding of elevated levels of red cell, platelet, leukocyte and endothelial cell-derived microparticles in PV patients vis-à-vis secondary polycythemics and healthy controls suggested microparticle origin from the MPN-associated cell activation, inflammation and apoptosis.

Very importantly, the wealth of experimental data on pathogenesis of thrombotic events in MPNs has helped

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create an evidence-based platform for the rational use of cyto-reductive and other therapies in these disorders. Pascale et al. [14] established that ET patients whose thromboxane A2 synthesis was insensitive to standard once-daily low dose aspirin (a regimen that is otherwise adequately anti-thrombotic in many high cardiovascular risk settings) would benefit from increased frequency of drug intake rather than an increase in dose. This deduction was made elegantly using enzyme immunoassays for arachidonic acid metabolites as well as the immature platelet fraction and mean and distribution of platelet volume, the Verify-Now assay, the glycocalicin index (indicating peripheral platelet destruction), light transmission platelet aggregometry and various other markers of inflammation and lipid peroxidation [14]. Similarly, both hydroxycarbamide and interferon alpha therapy reduce thrombotic risk not just by inhibiting proliferation of pluripotent hematopoietic progenitors, but also by decreased endothelial adhesion molecule expression and enhanced NO production in the case of hydroxyurea and neutralization of pro-inflammatory and atherogenic cytokines like PDGF-beta and TGF-beta in the case of interferon-alpha [15, 16].

Although the current Turkish study [1] had a relatively small sample size, it revealed some unusual findings. The *JAK2* mutation's presence modulated thrombotic risk prior to diagnosis, but not subsequently, suggesting a neutralization of its effect by effective therapy. Patient with higher allele burdens tended to have arterial, rather than venous thromboses, an association that has been debated upon in the past [6, 7]. Comparing with Indian data, one prior north Indian study had found a 25 % incidence of thrombosis in PV, with 50 % cases each being arterial and venous in nature [17]. *JAK2* V617F testing is now widely available, and several Indian laboratory-based studies have evaluated it in various settings [18]. Experimental data however, remain scarce, a lacuna that needs to be addressed by Indian scientists. The information would be especially valuable as availability of newer pharmacological modulators of the *JAK2* kinase increases in future.

References

1. Uyanik MS, Baysal M, Pamuk GE, Maden M, Akker M, Umit EG, Demir M, Aydogdu E (2015) Is JAK2V617F mutation the only factor for thrombosis in Philadelphia-negative chronic myeloproliferative neoplasms? Indian J Hematol Transfus Med. doi:10.1007/s12288-015-0578-2
2. Elliott MA, Tefferi A (2005) Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. Br J Haematol 128:275–290
3. Barbui T, Finazzi G, Carobbio A, Thiele J, Passamonti F, Rumi E, Ruggeri M, Rodeghiero F, Randi ML, Bertozzi I, Gisslinger H, Buxhofer-Ausch V, De Stefano V, Betti S, Rambaldi A, Vannucchi AM, Tefferi A (2012) Development and validation of an International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). Blood 120:5128–5133
4. Borowczyk M, Wojtaszewska M, Lewandowski K, Gil L, Lewandowska M, Lehmann-Kopydłowska A, Kroll-Balcerzak R, Balcerzak A, Iwoła M, Michalak M, Komarnicki M (2015) The JAK2 V617F mutational status and allele burden may be related with the risk of venous thromboembolic events in patients with Philadelphia-negative myeloproliferative neoplasms. Thromb Res 135:272–280
5. Marchetti M, Castoldi E, Spronk HM, van Oerle R, Balducci D, Barbui T, Rosing J, Ten Cate H, Falanga A (2008) Thrombin generation and activated protein C resistance in patients with essential thrombocythemia and polycythemia vera. Blood 112:4061–4068
6. Barbui T, Finazzi G, Falanga A (2013) Myeloproliferative neoplasms and thrombosis. Blood 122:2176–2184
7. Falanga A, Marchetti M (2012) Thrombotic disease in the myeloproliferative neoplasms. Hematol Am Soc Hematol Educ Program 2012:571–581
8. Barbui T, Carobbio A, Finazzi G, Vannucchi AM, Barosi G, Antonioli E, Guglielmelli P, Pancrazzi A, Salmoiraghi S, Zilio P, Ottomano C, Marchioli R, Cuccovillo I, Bottazzi B, Mantovani A, Rambaldi A, AGIMM and IIC Investigators (2011) Inflammation and thrombosis in essential thrombocythemia and polycythemia vera: different role of C-reactive protein and pentraxin 3. Haematologica 96:315–318
9. Panova-Noeva M, Marchetti M, Buoro S, Russo L, Leuzzi A, Finazzi G, Rambaldi A, Ottomano C, Ten Cate H, Falanga A (2011) JAK2V617F mutation and hydroxyurea treatment as determinants of immature platelet parameters in essential thrombocythemia and polycythemia vera patients. Blood 118:2599–2601
10. Marchetti M, Tartari CJ, Russo L, Panova-Noeva M, Leuzzi A, Rambaldi A, Finazzi G, Woodhams B, Falanga A (2014) Phospholipid-dependent procoagulant activity is highly expressed by circulating microparticles in patients with essential thrombocythemia. Am J Hematol 89:68–73
11. Villani L, Bergamaschi G, Primignani M, Rosti V, Carolei A, Poletto V, Catarsi P, Spolverini A, Vannucchi AM, Barosi G (2012) JAK2 46/1 haplotype predisposes to splanchnic vein thrombosis-associated BCR-ABL negative classic myeloproliferative neoplasms. Leuk Res 36(1):e7–e9
12. Teofili L, Martini M, Iachininoto MG, Capodimonti S, Nuzzolo ER, Torti L, Cenci T, Larocca LM, Leone G (2011) Endothelial progenitor cells are clonal and exhibit the JAK2(V617F) mutation in a subset of thrombotic patients with Ph-negative myeloproliferative neoplasms. Blood 117:2700–2707
13. Tan X, Shi J, Fu Y, Gao C, Yang X, Li J, Wang W, Hou J, Li H, Zhou J (2013) Role of erythrocytes and platelets in the hypercoagulable status in polycythemia vera through phosphatidylserine exposure and microparticle generation. Thromb Haemost 109:1025–1032
14. Pascale S, Petrucci G, Dragani A, Habib A, Zaccardi F, Pagliaccia F, Pocaterra D, Ragazzoni E, Rolandi G, Rocca B, Patrono C (2012) Aspirin-insensitive thromboxane biosynthesis in essential thrombocythemia is explained by accelerated renewal of the drug target. Blood 119:3595–3603
15. Maugeri N, Giordano G, Petrilli MP, Fraticelli V, de Gaetano G, Cerletti C, Storti S, Donati MB (2006) Inhibition of tissue factor expression by hydroxyurea in polymorphonuclear leukocytes from patients with myeloproliferative disorders: a new effect for an old drug? J Thromb Haemost 4:2593–2598

16. Silver RT, Kiladjian JJ, Hasselbalch HC (2013) Interferon and the treatment of polycythemia vera, essential thrombocythemia and myelofibrosis. Expert Rev Hematol 6:49–58
17. Varma S, Sharma A, Malhotra P, Kumari S, Jain S, Varma N (2008) Thrombotic complications of polycythemia vera. Hematology 13:319–323
18. Sazawal S, Bajaj J, Chikkara S, Jain S, Bhargava R, Mahapatra M, Saxena R (2010) Prevalence of JAK2 V617F mutation in Indian patients with chronic myeloproliferative disorders. Indian J Med Res 132:423–427