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COMMENTARY

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Possible interesting link between Janus kinase 2 mutation and renovascular hypertension

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Hypertension is highly prevalent worldwide and is one of the major risk factors for cardiovascular and renal diseases.[1] Experimental and clinical evidence has indicated that excessive activation of the renin-angiotensin system (RAS) in local tissue may mediate the development and progression of essential hypertension and the related target organ damage. Multiple studies have proven the usefulness of RAS blockade induced by ACE inhibitor and ARB for the management of essential hypertension.[2,3] Secondary hypertension accounts for ~10% of hypertensive patients; common etiological factors for secondary hypertension include renal parenchymal hypertension, primary aldosteronism (PA), renovascular hypertension, and sleep apnea syndrome hypertension.[2,3] Concerning renovascular hypertension, renal artery stenosis-related hyperactivity of the RAS directly contributes to an increase in blood pressure, and recent studies indicate that the existence of functional RAS with its components expression in the circulating blood cells such as leukocytes, suggesting a possible relationship between hypertensive disease and hematologic disorders.[4]

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders characterized by expansion of one or more myeloid cell lineages; and, particularly in polycythemia vera (PV) and essential thrombocythemia (ET), a tyrosine kinase Janus kinase 2 (JAK2) pathway reportedly plays a significant role in the pathogenesis of MPNs. PV and ET, subtypes of MPNs, create high risk for thrombotic events and occlusive vascular diseases, including myocardial infarction and stroke. These complications are the main cause of death among PV and ET patients, highlighting the importance of prevention and management of the condition. However, recommendations for the management of MPNs, such as PV and ET, are based on thrombotic risk, and a limited number of randomized clinical trials and observational studies described the clinical course of the disease and indirectly evaluated the role of different treatments.[5] Thus, evidence from prospective clinical trials is limited and clinical expertise still plays a major role in guiding the therapy of patients with this disease.[5]

Concerning the blood pressure dysregulation in MPNs, several forms of hypertensive disease, including portal hypertension, pulmonary hypertension, and systemic hypertension, occur as a complication of MPNs.[5-10] Also, several cases of renovascular hypertension and renal artery stenosis in MPNs patients have been described.[11-16] However, in spite of recent progress in the diagnosis and treatment strategy of renovascular hypertension and renal artery stenosis,[17-19] the common clinical manifestations of patients with MPN-associated renovascular hypertension are unclear and optimal treatment strategy for the renovascular lesion in such patients are undetermined.

In this issue of *Journal of Clinical Hypertension*, Mishima E et al[20] reported 2 interesting cases of renovascular hypertension associated with JAK2 mutation-positive MPNs in which renal artery angioplasty effectively ameliorated the hypertension. Concerning the mechanistic link between MPNs and the pathogenesis of renal artery stenosis, the authors showed that the stenotic lesions in the renal arteries were radiographically considered to be thrombotic plaque or intimal hyperplasia, which would be associated with PV and ET.[20] In addition, since JAK2 signaling activates STAT and subsequently drives activation of

platelets and leukocytes and accelerates hyperplasia of the vascular cells, leading to atherosclerotic plaque and intimal hyperplasia, the authors suggest that constitutive activation of the JAK-STAT pathway is another possible mechanism.[20] Although a high JAK2 V617F allele burden may be associated with the increased risk of renovascular hypertension in patients with MPNs as another attractive hypothesis for mechanistic link, the authors did not evaluate the allele burden in the present cases.[20] The functional modulation of JAK2 function would be a possible strategy for the amelioration of the vascular complication, including renal artery stenosis as well as MPNs, and unidentified factor(s) may play a critical role in mediating the mechanistic link between renovascular hypertension and MPNs; therefore, in order to further improve the efficacy of therapeutic strategy for serious vascular complications in MPNs, further investigative efforts are necessary to identify the precise molecular mechanism of the pathological interaction between altered JAK2 function and its effect on the modulation of circulating blood cell function and vascular homeostasis.

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CONFLICT OF INTEREST

The authors declared that they do not have any conflicts of interest with respect to this manuscript.

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