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REVIEW

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Excess is Trouble: Polycythemia vera entrapped organs and hypertension

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Abstract

The 2013 updated risk stratification data for thrombosis in polycythemia vera (PV) not only considered the well-known roles of advanced age and thrombosis but additionally suggested importance of the cardiovascular risk factors, one of them being hypertension. In the present narration on PV and hypertension, literature of case studies or patients series describing the association of arterial, pulmonary, renovascular and portal hypertension have been documented in addition to the reports highlighting independent pathogenic mechanism of the disease contributing to hypertension. This in turn emphasises diagnosis of hypertension at early stage and its management to decrease the risk of thrombosis in PV.

Keywords: *myeloproliferative disorders; myeloproliferative neoplasms; pulmonary hypertension; renovascular hypertension; portal hypertension*

Introduction

Polycythemia vera (PV), classified under myeloproliferative disorders (MPDs) and subsequently myeloproliferative neoplasms (MPNs) by World Health Organization in 2008 are with laboratory hallmark of increased red cell mass. There is also often an increase in white cell count, platelet count, and leukocyte alkaline phosphatase along with other findings reflecting the increased rate of turnover of hematopoietic cells. The bone marrow biopsy generally displays hypercellularity involving all three cell lines and absence of iron stores [1,2]. The diagnosis of PV depends on excluding spurious polycythemia in which there is a high hematocrit but a normal red cell mass and secondary polycythemia in which there is an increased red cell mass in response to tissue hypoxia or the inappropriate production of erythropoietin, generally by a tumor [3]. Another characteristic finding is the expression of the Janus Kinase 2 (JAK2) mutation, V617F. This mutation in exon 12 of the JAK gene is responsible for the uncontrolled cell proliferation in 90% of PV patients and in about 50% of patients with essential thrombocythemia /essential thrombocytosis (ET) and idiopathic myelofibrosis /primary myelofibrosis (PMF) also called Philadelphia chromosome negative MPDs [2,4]. In people with PV, due to the defective JAK2 gene, its overactive protein, non-receptor tyrosine kinase causes hematopoietic stem cells to grow and divide even in the absence of erythropoietin, clogging the bone marrow. These cells break down and die and form scar tissue [2]. The disorder is estimated to affect approximately 2 people per 100,000 in general population. Although, it occurs most often in individuals with age more than 60 years and is rare in individuals under 20, it can affect individuals of any age. It is more common in males than in females, but females within the reproductive age range are more affected [2].

The symptoms of PV occur because of overproduction of RBCs and, to a lesser extent, the overproduction of white blood cells and platelets. It is associated with reduced survival because of cardiovascular complications and progression to post-PV myelofibrosis or leukemia. Controlled trials have demonstrated that incidence of cardiovascular events is reduced by sustained control of hematocrit with phlebotomies and occasionally plateletpheresis (low-risk patients) and/or cytotoxic agents (high-risk patients) and antiplatelet therapy with aspirin mainly to improve the circulation of blood by lowering the blood viscosity. Hydroxyurea and interferon may be used as first-line treatments, whereas busulfan, a cell cycle non-specific alkylating antineoplastic agent, is reserved for patients that are refractory or resistant to first-line agents [5].

The overproduction of RBCs in the marrow and subsequently high numbers in the circulation (red blood mass) leads to thickening of the blood and increase in the volume causing a condition called hyperviscosity. Thickened blood may not flow through smaller blood vessels properly. A variety of symptoms can occur in individuals with PV including nonspecific symptoms such as headaches, fatigue, weakness, dizziness or itchy skin; an enlarged spleen (splenomegaly); a variety of gastrointestinal issues; and the risk of blood clot formation, which may prevent blood flow to vital organs. There are a variety of nonspecific symptoms at onset related to the increased red cell mass and hematocrit accompanied by the more specific manifestations of pruritus (or itch), erythromelalgia (a rare condition that primarily affects the feet and, less commonly, the hands [extremities] with burning pain, severe redness and increased episodic or continuous high temperature) and hepatic, portal, and mesenteric vein thrombosis. Splenomegaly and hypertension are also common [2]. Thromboembolic events occur in about 27% of the patients with PV and account for 31% of the deaths. These include cerebrovascular accidents, myocardial infarction, peripheral vascular occlusions, pulmonary infarctions, and venous thrombosis [6]. Pósfai É, et al. have demonstrated thrombosis in female patients with MPDs and documented that female PV patients with high blood pressure, hyperlipidaemia and/or cigarette smoking may be at a higher risk of thrombotic events and require special consideration of prevention and management of thrombotic events [1]. Among these CV risk factors, hypertension

in PV has also been identified as consequence of the inbuilt pathogenic feature of the disease. The reports are unfolding its de novo existence with the disease and not just as association due to some other cause.

Polycythemia vera and hypertension

Gaisböck's original observation of the association of polycythemia and hypertension was revisited by Krishnamoorthy P et al. (2018) They aimed to study the relationship between polycythemia and cardiac risk factors using a large national registry. In their study, PV patients of age more than 18 years with a diagnosis of polycythemia were identified from the National Inpatient Sample 2009-2010 database using International Classification of Diseases; Ninth Edition (ICD-9) code 238.4. Demographics, cardiac risk factors, and cardiovascular events were identified. These PV patients had a significantly increased prevalence of all cardiac risk factors and events, except for diabetes mellitus and chronic kidney disease. Hypertension was more prevalent in polycythemia compared to controls (61 vs. 46%; P<0.0001). After adjusting for age, sex, race, diabetes mellitus, hyperlipidemia, tobacco use, obesity, coronary artery disease, heart failure, and chronic kidney disease, polycythemia was still a determinant of hypertension [1.37 (1.28-1.45); P<0.001]. Polycythemia in this study had high prevalence of all cardiac risk factors but was independently associated with increased prevalence of hypertension even after adjusting [7]. Barbui T et al. (2014) have also documented similar findings. They concluded that among cardiovascular risk factors (smoking, diabetes mellitus, hypercholesterolemia), arterial hypertension had the most relevant prognostic role for the incidence of arterial thrombosis in PV patients, conventionally identified as low risk for future complications [8].

An interesting study by Vrsalovic MM et al. in 2007 have shown that in bone marrow of PV patients, renin angiotensin system (RAS) was overexpressed and led to hypertension and in addition RAS also stimulated bone marrow hematopoietic progenitor cells [9]. Support to this study was already documented in 2002 by Plata R et al. who had demonstrated that in altitude polycythemia, enalapril, an ACE inhibitor, not only decreased blood pressure but also packed cell volume and haemoglobin concentration [10]. Similar findings were also reported by Gaston RS et al. in early nineties (1994) wherein ACE inhibitors were shown to decrease blood pressure, packed cell volume and haemoglobin concentration in polycythemia that followed renal transplantation [11]. These studies underlined that ACE inhibitors have been useful not only in decreasing arterial hypertension but also in controlling cell production [12] and thus endorse association of hypertension with thrombotic events and eradication of hypertension in PV to control thrombotic events.

In addition to the role of RAS, biochemical mechanism in PV, in causing elevation of blood pressure was put forth in 2014 by Rusak T et al. They demonstrated a direct association of cell haemoglobin released from erythrocytes (cell-free haemoglobin, fHb) with hypertension. They assessed hematocrit, mean arterial pressure (MAP), blood viscosity, and the level of fHb and nitrite/nitrate (NOx) in the plasma of 73 PV patients and 38 healthy controls. The effect of isovolemic erythrocytapheresis (ECP) on the considered parameters was also studied. It was found that in comparison with healthy controls, PV patients had significantly ($p \leq 0.01$) elevated haematocrit (0.567 vs. 0.422), blood viscosity (5.45 vs. 3.56 cP), MAP (106.8 vs. 93.8 mmHg), plasma fHb (9.7 vs. 2.8 mg/dL), and NOx levels (34.1 vs. 27.5 μM). In PV patients, fHb positively correlated with MAP (r = 0.489), NOx levels (r = 0.461), hematocrit (r = 0.428), and viscosity (r = 0.393). Haematocrit positively correlated with blood viscosity (r = 0.894), but poorly with MAP. In fact the correlation between MAP and NOx altered from - 0.325 (healthy control) to + 0.268 (PV patients). ECP procedure was associated with a significant ($p < 0.01$) reduction of hematocrit, fHb, blood viscosity, and MAP. These 73 PV patients were divided into a subset of subjects with normal (normotensive patients, n = 16) and elevated MAP (hypertensive patients, n = 57). Compared with normotensive patients, hypertensive PV patients demonstrated a higher rise in fHb (10.2 vs. 8.0) and plasma NOx levels (35.8 vs. 31.0). In the normotensive subgroup of PV patients the ECP procedure did not affect MAP. It was concluded that accelerated scavenging of nitric oxide by fHb rather than high hematocrit was most probably a key factor determining the development of hypertension in PV patients [13].

Way back in 1992 Reisner SA et al. had also demonstrated cardiac involvement in patients with myeloproliferative disorders by two-dimensional Doppler echocardiography. The authors concluded that the heart was frequently involved in patients with MPD, particularly when their past history was complicated by a thromboembolic event. Some patients had clinically significant valvular disease. In this study pulmonary hypertension was found to be another relatively common finding in MPD patients [14].

Pulmonary hypertension (PH)

It is a severe hemodynamic disorder in which the pulmonary artery pressure is persistently elevated, leading to right-sided heart failure. Some studies have suggested an association between PH and MPDs. MPN-associated PH, is included in group five of the most recent clinical classification of PH and has been reported to be associated with MPN, affecting 5-48% of these patients [15]. Tachibana T et al. (2017) have reported a case in Japan of association of PH with pulmonary Veno-occlusive disease in patients with PV. Right heart catheterization, radiographic findings and resistance to pulmonary vasodilators led to the diagnosis of PH associated with pulmonary veno-occlusive disease. They further suggested that PH should be considered a potential complication and screened during the clinical care of patients with MPNs [16].

The hypoxic response is a stress response triggered by low oxygen tension. Hypoxia induced factors (HIFs) play a prominent role in the pathobiology of hypoxia-associated conditions, including PH and polycythemia. The c-Jun N-terminal protein kinase (JNK), a stress-activated protein kinase that consists of two ubiquitously expressed isoforms, JNK1 and JNK2, and a tissue-specific isoform, JNK3, have been shown to be activated by hypoxia. The physiological role of JNK1 and JNK2 in the hypoxic response was studied by Sala MA et al. (2018). They further demonstrated physiological role of JNK2 and HIFs in contributing hypoxia induced erythropoiesis and PH. Here, using genetic knockout cells and/or mice, they showed that JNK2, but not JNK1, up-regulated the expression of HIF-1α and HIF-2α that contributed to hypoxia-induced PH and polycythemia. Knockout or silencing of JNK2, but not JNK1, prevented the accumulation of HIF-1α in hypoxia-treated cells. Loss of JNK2 resulted in a decrease in HIF-1α and HIF-2α mRNA levels under resting conditions and in response to hypoxia. Consequently, hypoxia-treated Jnk2-/- mice had reduced erythropoiesis and were less prone to polycythemia because of decreased expression of the HIF target gene erythropoietin (Epo). Jnk2-/- mice were also protected from hypoxia-induced PH, as indicated by lower right ventricular systolic pressure, a process that depends on HIF. Taken together, their results suggested that JNK2 is a positive regulator of HIFs and therefore may contribute to HIF-dependent pathologies, one of them being PH [17].

Pulmonary extra-medullary hematopoiesis and pulmonary hypertension from underlying PV

Pulmonary extra-medullary hematopoiesis (EMH) refers to the presence of hematopoietic precursor cells in the lung. It is a rare complication associated with myelofibrosis. In a case series Singh I et al. (2017) have highlighted the clinical-pathological-radiological features of pulmonary EMH and PH from underlying PV [18].

Renovascular hypertension

Previous case reports have documented a link between primary or secondary polycythemia and the presence of renal artery stenosis and renovascular hypertension. Renal artery stenosis is the narrowing of the renal artery which causes hypertension and atrophy of the affected kidney, ultimately leading to renal failure if not treated and most often caused by atherosclerosis or fibromuscular dysplasia [19]. Renal artery stenosis has also been documented in patients with the antiphospholipid syndrome and in very few cases with MPDs. In a paper by Zahra Ha-ou-Nou F et al. investigation of a 31-year-old female with a history of gangrene affecting the toes with severe hypertension (200/110 mmHg), revealed a combination of renal artery stenosis, primary antiphospholipid syndrome and PV [20].

Portal hypertension

MPD is an important cause of thrombosis of the hepatic and portal venous system as well. The diagnosis in many of these patients is missed as they have an atypical clinical presentation and may have a normal haematological profile at presentation.

Many trials report identification of an underlying myeloproliferative neoplasm by investigation of the patients developing portal hypertensive oesophagus and/or fundus variceal hemorrhage in the absence of any known etiology. Toros AB (2013) et al. detected portal hypertension in 13.8% of the MPN patients (n = 4), prevalence similar to other studies published at that time. They further concluded that considering the fact that diagnosis of MPNs usually takes a long time, treatment should be started right after the diagnosis has been confirmed by bone marrow biopsy or cytogenetic studies [21]. Pati HP et al. (1998) reported a case history of 30-year-old patient with features of portal hypertension due to extrahepatic portal venous obstruction. She had a normal haemoglobin level and haematocrit at presentation, but the red cell mass was found to be elevated even in the presence of low serum iron levels. A diagnosis of polycythaemia vera as the underlying disease was made [22]. In 1990 Wanless IR have reviewed the autopsy findings and clinical histories of 97 patients with PV and 48 patients with agnogenic myeloid metaplasia (A progressive, chronic disease in which the bone marrow is replaced by fibrous tissue and blood is made in organs such as the liver and the spleen, instead of in the bone marrow) collected from three institutions and from the PV Study Group. Cirrhosis was present in seven patients, one of whom had bleeding varices. Esophageal varices were present clinically in 10 patients without cirrhosis (seven polycythemia and three agnogenic myeloid metaplasia). All of these patients had lesions in small or medium-sized portal veins and four had stenosis of the extrahepatic portal vein with histology compatible with organized thrombi. Nodular regenerative hyperplasia occurred in 14.6% and correlated closely with the presence of portal vein lesions. Thirty patients had greater than 500 ml of ascites, seven of these patients also had varices and six of them had hepatic vein thrombosis. Ascites also correlated with hepatic vein disease confined to small intrahepatic branches. No correlation was seen between hepatic hematopoietic infiltration and signs of portal hypertension. They concluded that esophageal varices were common and were almost always associated with portal vein lesions visible by light microscopy. These portal vein lesions, the secondary effects of nodular regenerative hyperplasia and portal hypertension, were most likely a result of portal vein thrombosis in patients with MPDs [23]. Baniel J et al. (1989) described a case history of a patient known to have PV who developed recurrent melena (black tarry stool, which occurs as a result of upper gastrointestinal bleeding) and was found to have bleeding gastroesophageal varices. Selective superior mesenteric angiography suggested splenic vein thrombosis. Splenectomy led to the disappearance of the varices with no subsequent recurrence of bleeding. They believed this to be the first fully described case of PV associated with segmental portal hypertension, and proposed that PV patients may develop "silent" segmental portal hypertension and that this should be taken into consideration when treating them [24].

Current classifications of the thrombotic risk in patients with PV, do not predict cardiovascular risk, and this condition does not currently influence the choice of cytoreductive therapy. Diagnosis of PV requires as major criteria, the increase of hemoglobin/hematocrit ratio, whose threshold levels have been established by 2016 World Health Organization (WHO) revised criteria (>16.5 g/dL or >49% for males and >16 g/dL or >48% for females), the presence of JAK2 mutation, and the bone marrow tri-lineage proliferation [25,26]. To date cardiovascular risk factors have not been integrated in the widely used risk guided management of PV. It is still based on only two risk factors (age and prior thrombotic events) and classified patients into low (age <60 years without prior thrombotic event) and high risk (age > 60 years with/without prior thrombotic events) categories. However, many factors can contribute to promoting the thrombotic event due to the interaction between platelets, leukocytes, and endothelium alterations. Moreover, a significant role can be played by cardiovascular risk factors such as hypertension and others for e.g. cigarette smoking habits, diabetes, obesity and dyslipidemia as well.

The evidence continues to emerge. Cerquozzi et al. (2017) have explored the association of cardiovascular risk factors with the occurrence of arterial or venous events. They found that older age (≥ 60 years), hypertension, diabetes, hyperlipidemia, and normal karyotype were associated with arterial events, whereas younger age (< 60 years), female sex, palpable splenomegaly, and history of major hemorrhage were associated with venous events [27]. A study carried out by Nervekar et al. (2019) on Clinical Spectrum and Complications of Polycythemia, in patients presenting at Tertiary Care Centre at Goa demonstrated that hypertension was found to be frequently associated with Vera as well as in secondary causes due to obstructive sleep apnoea (OSA) [28]. A recent study by Accurso V et al. (2020) analysed PV patients (n.165) (0.3 – 289.30 months), wherein the correlation of cardiovascular risk conditions with the onset of thrombosis has been evaluated. They have demonstrated that in patients with PV, the frequency of thrombotic episodes was strictly correlated with cardiovascular risk factors; in fact, the frequency of thrombosis was much lower in patients without cardiovascular risk [29].

Conclusion

As depicted in this manuscript, literature has single case reports as well as series of PV patients' data on presence of hypertension (pulmonary, renovascular or portal) as one of the important clinical finding associated with this disease. This emphasises to include the diagnosis and steps for its management simultaneously. Being an early pathogenic event, diagnosis and treatment of hypertension as

well as management of other cardiovascular risk factors, earlier, can prevent the very fatal thrombotic event in these patients.

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