REGULAR ARTICLE

Hematologic Disorders and Pulmonary Hypertension

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INTRODUCTION

Group 5 pulmonary hypertension (PH) has long remained an elusive entity. Data over the past decade have consistently shown links between hematologic disorders and pulmonary vascular disease. PH due to hematologic disorders exemplifies how pulmonary vascular disease is intertwined with vascular abnormalities at the systemic level.

At the last (6th) World Symposium on PH in 2018, Group 5 PH was defined as "PH with unclear and/or multifactorial mechanisms," and PH secondary to hematologic disorders forms Subgroup 5.1 (Table 1).[1] This subgroup includes 2 primary and very important etiologic entities, namely chronic hemolytic anemias and myeloproliferative disorders, both of which will be discussed in detail. Postsplenectomy PH was previously considered a unique subgroup in this category. However, at the 6th World Symposium, it was deemed a risk factor, rather than a unique clinicopathologic entity, given its role in the development of PH in other hematologic conditions, such as β-thalassaemia,[2] or in chronic thromboembolic PH (CTEPH, Group 4 PH).[3]

MYELOPROLIFERATIVE DISORDERS

The 2008 World Health Organization classification of chronic myeloproliferative disorders include multiple entities as listed in Table 2.[4] Of these, patients with chronic myelogenous leukemia, polycythemia vera (PV), primary myelofibrosis, and essential thrombocythemia (ET) are at particularly high risk of PH.

Prevalence of PH in myeloproliferative disorders (MPDs)

Several small studies have evaluated PH via echocardiography (defined as a right ventricular systolic pressure >35 mm Hg) in myeloproliferative disorders (MPDs) with a widely variable estimated prevalence. Two studies in cohorts of under 50 patients each reported echocardiographic PH prevalence rates of over 40% in ET.[5,6] More recently, larger studies have reported lower prevalence rates, although higher when compared to the general population. For instance, in a 2020 study by Lopez-Mattei et al,[7] out of 143 patients with myelofibrosis, 14% had echocardiographic PH, and these patients had significantly elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Similarly in a study screening 183 MPD patients with transesophageal echocardiograms (TTEs), 7.7% were found to have echocardiographic signs of PH.[8] However, in a recent meta-analysis examining 17 studies evaluating PH in MPDs, it was found that studies using TTE estimated a prevalence of 5-fold higher than those using right heart catheterization for the PH diagnosis.[9]

Etiopathogenesis of PH in MPDs

PH in MPDs develops via multiple pathologic mechanisms resulting in unique phenotypes.

CTEPH is one of the most prominent phenotypes in MPD patients. MPDs induce a state of hypercoagulability, historically widely reported in PV and ET and more recently even in myelofibrosis. In a seminal study that followed over 1200 PV patients over a 20-year period, arterial and venous thrombotic events were reported in 41% patients, with nearly 64% of these occurring at or prior to diagnosis of PV.[10] Studies in ET have reported thrombotic rates of nearly 30% and myelofibrosis around 11%.[11]

Table 1. Group 5: PH With Unclear and/or Multifactorial Mechanisms[a]

5.1 Hematological disorders • chronic hemolytic anemias • myeloproliferative disorders (MPDs)
5.2 Systemic and metabolic disorders (eg, Gaucher disease)
5.3 Other disorders including fibrosing mediastinitis
5.4 Complex congenital heart disease

[a]Adapted after Simonneau et al.[1]

Table 2. WHO Classification of Myeloproliferative Neoplasms[a]

Chronic myelogenous leukemia, *BCR-ABL1*–positive
Chronic neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis
Essential thrombocythemia
Chronic eosinophilic leukemia, not otherwise specified
Mastocytosis
Myeloproliferative neoplasms, unclassifiable

[a]Adapted after Vardiman et al.[4]

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In addition to high platelet count or red blood cell counts directly induced thrombosis, hyperviscosity is a major independent risk factor. Differential peripheral displacement of platelets in high red blood cell load states causes shear-induced platelet activation and consequent thrombosis.[12] Altered red blood cell and leukocyte membrane structure also promote clot formation in MPDs as does polymorphonuclear leukocyte activation due to Janus Kinase-2 mutations. In addition to large clot burden, microscopic tumor emboli also form within the pulmonary vasculature. Age, prior thrombotic events, cardiovascular risk factors[13] and the presence of inherited thrombophilia such as the Factor V Leiden mutation, all further increase the risk of thrombotic events in these patients. As mentioned previously, splenectomy, often used in the therapy of certain hematologic disorders, can induce a hypercoagulable state. In a study evaluating postsplenectomy portal venous thrombosis, a 2% rate was reported, with this number rising up to 10% in patients with underlying hematologic diseases.[14]

Drug-induced PH in MPDs is also an important entity. Tyrosine-kinase inhibitors, which are frequently used in MPD therapy, have been implicated by several studies and have been associated with precapillary forms of PH, resembling Group 1 pulmonary arterial hypertension (PAH). In the French PH registry, a PH incidence rate of 0.45% was reported in chronic myelogenous leukemia patients treated with dasatinib. Clinical or hemodynamic improvements were reported with drug discontinuation in the majority of these patients.[15] Several other drugs in the tyrosine-kinase inhibitor class have been associated with PH in smaller studies. In addition, chemotherapy-induced pulmonary veno-occlusive disease is now an increasingly recognized cause of pulmonary vascular disease. A 2016 study evaluating patients with pulmonary veno-occlusive disease in the French registry revealed that 83.8% of these patients had been exposed to alkylating agents, with 43.2% having received cyclophosphamide.[16] Bone marrow transplantation can also amplify the risk of pulmonary veno-occlusive disease in the MPD population.[17]

Portopulmonary hypertension is one other potential cause of pulmonary vascular disease in MPDs. Portal hypertension was reported in 13.8% of serial patients with PV, ET, and myelofibrosis seen at a hematology clinic.[18] In a meta-analysis of studies reporting hepatic vascular thrombosis in hematologic neoplasms, the mean prevalence of MPDs and Janus Kinase-2 mutations was 31.5% and 27.7% in patients with portal venous thrombosis.[19] While not all portal venous thromboses result in portopulmonary hypertension, it does increase the risk of its occurrence in these patients. In addition to thrombotic complications, direct extramedullary hematopoiesis in the portal vasculature has been postulated as a mechanism of portal thrombosis.[20]

Pulmonary extramedullary hematopoiesis and myeloid metaplasia has also been described within pulmonary vasculature of MPD patients, leading not only to an obstructive physiology, but also an inflammatory vascular remodeling simulating PAH arteriopathy.[21]

Management of MPD-PH

To date, there are no data or clinical trials evaluating PAH-specific therapy in MPD-PH. The focus of therapy remains the treatment of the underlying hematologic pathology. There are no specific data or society recommendations on additional anticoagulation or antiplatelet therapy in this population either. For instance, in PV, antiplatelet prophylaxis is standard of care, but its impact on pulmonary venous thromboembolism and PH remain unclear as does the role of additional anticoagulation. While cytoreductive therapy such as hydroxyurea can be used in high-risk patients to prevent thrombotic events, data on its effect on pulmonary vascular pathology remain limited to isolated case reports.[22] Similarly, mitigation of PAH postallogenic bone marrow transplant in myelofibrosis has been reported, but robust studies remain lacking.

In a case series by Guilpain et al[23] in 2008 reporting the clinical features and management of 10 patients with MPD PH, 6 were found to have CTEPH and 4 with other forms of MPD PH. All 4 patients with proximal CTEPH had an underlying diagnosis of PV. Three of these successfully underwent thromboendarterectomy and 1 with end-stage right heart failure was treated with a combination of surgery and inhaled iloprost but eventually died of right heart failure. Two patients with distal CTEPH were medically managed with bosentan, 1 of whom died of right heart failure. All patients were treated with cytoreductive therapy +/- phlebotomy. Among the 4 patients with non-CTEPH MTD PH, all received cytoreductive therapy and only 1 received PAH-specific therapy with epoprostenol. All 4 died, 2 of whom from right heart failure. While riociguat is currently the only approved therapy of nonoperative CTEPH (Group 4 PH), there are no specific studies or recommendations for the treatment of CTEPH in the setting of MPDs.

In the recent past, there has been interest in the use of Janus Kinase-2 inhibitors in MPD PH. In 15 patients with myelofibrosis and echocardiographic parameters of PH, improvements were seen in NT-proBNP and right ventricle (RV) function post therapy with ruxulotinib, but not with other conventional agents.[24] In addition, recent preclinical data in PH animal models have shown that ruxolitinib attenuates pulmonary artery smooth muscle cell proliferation and improves pulmonary hemodynamics and RV remodeling. These data taken together are indicative that the Janus Kinase-2 pathway may be of special interest in the niche subset of MPD PH as a novel therapeutic target.

CHRONIC HEMOLYTIC ANEMIAS

Of the chronic hemolytic anemias (CHAs), several entities have been associated with PH, such as paroxysmal nocturnal hemoglobinuria, hereditary spherocytosis, sickle cell disease (SCD) and thalassemia, the latter 2 being associated with a much heavier pulmonary disease burden.

Prevalence of PH in CHAs

Several studies have reported mortality correlations with tricuspid regurgi-

tant jet velocity (TRV) and estimated pulmonary artery systolic pressure on TTE in SCD.[25] A study that screened 398 patients with SCD with TTE and then proceeded with right heart catheterization if the TRV was at least 2.5 m/s, reported a 27% prevalence of PH based on TTE and 6% (24 patients) when confirmed by right heart catheterization.[26] Among the 24 patients with PH, 11 had normal pulmonary capillary wedge pressures, indicating a precapillary arteriopathy. Similarly, in a study that screened echocardiographically 529 SCD patients with subsequent right heart catheterization in 84, precapillary PH was confirmed in 10.4% of patients. Of note, mean pulmonary artery pressure, diastolic pulmonary gradient, transpulmonary gradient, and pulmonary vascular resistance all independently correlated with mortality.[27] Median survival was 6.8 years in those diagnosed with precapillary PH. The ATS guideline statement for PH in SCD proposes an increased risk for mortality defined as a TRV ≥ 2.5 m/s, an NT-proBNP ≥ 160 pg/mL, or PH confirmed by right heart catheterization.[28] Echocardiographic screening per their recommendations should be performed every 1 to 3 years in adults. In patients with TRV ≥ 2.5 m/s, prior venous thromboembolism, more severe hemolysis or frequent pain crises, a shorter duration interval for repeat TTEs should be used. Guidelines from other bodies including the American Society of Hematology and the National Lung, Heart and Blood Institute vary and screening remains an area of controversy at this time.

Studies in thalassemia similarly report variable prevalence rates based on TTE vs right heart catheterization screening. However, a recent large multicenter study of over 1000 patients with β-thalassemia reported a PH prevalence of 2.1% based on invasive hemodynamics.[2]

Etiopathogenesis of CHA PH

PH in CHAs is multifactorial, involving a combination of factors ranging from direct effects of hemolysis and hypercoagulability to pulmonary vascular complications of CHA therapy.

Group 2 PH is common in this cohort because of restrictive cardiomyopathy and other risk factors for diastolic dysfunction[29] including hypertension, end stage renal disease, high output failure from anemia, etc. Hypercoagulability from the activation of prothrombotic factors in SCD and from asplenia increases the risk of CTEPH. Proposed pathogenic mechanisms of PH include depletion of nitric oxide by hemolysis-induced release of arginase-1, circulating free hemoglobin, endothelin-1 upregulation, and proliferative arteriopathy from vascular endothelial growth factor upregulation, all contributing to the dysfunction of the pulmonary vasculature.[30]

Management of CHA PH

Screening: As previously mentioned, the ATS guideline for SCD PH recommends echocardiographic screening every 1 to 3 years in adults. In high-risk patients (eg, high hemolytic burden), more frequent screening intervals are recommended. Based on several studies correlating TRV to SCD PH outcomes, the ATS proposes the following:

- In those with TRV ≤ 2.5 m/s: routine screening continued
- TRV 2.5 to 2.9 m/s: consider increased frequency of screening and escalate SCD therapies. If patients are symptomatic, have a decreased 6-minute walk distance or increase in NT-proBNP, then right heart catheterization is recommended.
- TRV ≥ 3: right heart catheterization for definitive diagnosis.

Therapy: Aggressive management of the underlying hematologic dyscrasia is recommended. Hydroxyurea is well described in SCD literature to reduce the incidence of thoracic complications including acute chest syndrome and should be initiated in patients with PH or evidence suggestive of pulmonary vascular disease such as an elevated NT-proBNP. Chronic transfusion therapy to maintain low levels of sickled red cells can be used in this population if hydroxyurea is contraindicated.[28] Supportive therapy such as supplemental oxygen and cautious diuresis (to prevent acute sickling) should be considered. Patients with SCD and PH are reported to have a higher risk of venous thromboembolism than SCD patients without PH.[31] However, SCD also carries an inherent risk of cerebral and other hemorrhagic events. Hence, as the guidelines stand, in patients with SCD PH without an elevated risk of bleeding, lifelong anticoagulation is recommended if diagnosed with current or prior thromboembolic events.[28]

Regarding PAH-specific agents, there have been very few directed clinical trials examining their use in SCD PH. The ASSET 1 and 2 trials, which evaluated bosentan in patients with SCD PAH and SCD pulmonary venous hypertension, respectively, reported a trend toward an increase in cardiac output and decrease in pulmonary vascular resistance. However, no conclusive results could be derived since the studies were prematurely terminated due to slow enrollment.[32]

The Walk-PHaSST study that evaluated the use of sildenafil in SCD PH confirmed by right heart catheterization was prematurely terminated for safety due to an increased risk of crises events.[33] As a consequence, PDE5 inhibitors are avoided in this population. Riociguat has been examined in a limited case series of SCD CTEPH and an improvement in 6-minute walk distance, pulmonary vascular resistance, and cardiac output was reported.[34] In a small case series reporting inhaled, subcutaneous, and parenteral prostanoids in patients with SCD PH and SCD CTEPH, an improvement in right ventricular systolic pressures was reported with variable change in functional status and 6-minute walk distance.[35]

CONCLUSIONS

PH associated with hematologic disorders remains a heterogeneous and challenging group of clinical entities. The relative rarity and/or variable clinical presentation of many of these disease processes has made it challenging to study these entities in randomized clinical trials and make recommendations of a unifying treatment that can be applied broadly. While the main focus for therapy is the underlying disease process, greater understanding may be gained from future preclinical studies focusing on identifying

the pathogenic mechanisms of pulmonary vasculopathy and the development of prospective registries.

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