Pulmonary Hypertension in Chronic Myeloproliferative Disorders

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Chronic myeloproliferative disorders (CMPDs) are a heterogenous group of disorders characterized by cellular proliferation of one or more hematologic cell lines in the peripheral blood. Bone marrow histology shows hypercellularity and fibrosis in most of these disorders. The incidence of CMPD is estimated between 6 and 9 new cases per 100,000 yearly. CMPDs are incurable and are associated with a variable clinical course. Pulmonary hypertension (PH) is a well-recognized complication of CMPD, and when present, portends a poorer prognosis with median survival as low as several months, though this varies by the type of PH as well as the severity of the underlying CMPD. This review will serve to summarize the current knowledge of epidemiology, pathophysiology, diagnostic methods, clinical implications, and management of PH in CMPD.

The first association between chronic myeloproliferative disorders (CMPDs) and pulmonary hypertension (PH) dates to the early 1990s, and has been cited as the most prominent cardiac disorder in myeloproliferative diseases (MPDs). However, the majority of information that exists is limited to case reports and retrospective case series. So, while causal links have been well established between these 2 diseases, the temporal sequence between CMPD and PH is still unknown.

PH is defined as a mean pulmonary artery pressure (mPAP) of ≥25 mm Hg by right heart catheterization (RHC) when at rest, and can present in association with a multitude of other disease processes, which are classified into the 5 World Symposium on PH (WSPH) diagnostic groups.[1] The fifth WSPH, held in 2013, in Nice, France, further delineated the hematologic disorders in Group 5, now identified as "pulmonary hypertension with unclear multifactorial mechanisms; subtype 5.1: hematologic disorders."[1,2]

CMPDs are a subset of the hematologic disorders. CMPDs refer to a group of hematopoietic disorders characterized by a clonal proliferation of one or more hematopoietic cell lineages, predominantly in the bone marrow, but can present in the liver or spleen. Additionally, extramedullary hematopoiesis, myelofibrosis, and transformation at varying rates to acute leukemia occur at increased rates in CMPD.[3] The CMPD World Health Organization (WHO) classification was revised in 2008, and divides CMPD into 7 categories: myeloproliferative neoplasms, myeloid and lymphoid neoplasms, myelodysplastic syndromes/myeloproliferative neoplasms, myelodysplastic syndromes, and acute myeloid leukemia.[4]

CMPD is associated with a variety of pulmonary complications, including PH.[5] This review will serve to summarize the current understanding of the epidemiology, pathophysiology, diagnostic methods, clinical implications, and possible therapeutic interventions of PH in CMPD.

EPIDEMIOLOGY

The incidence of CMPD is rare and estimated between 6 and 9 new cases per 100,000 per year, most commonly occurring between 40 and 60 years of age.[6,7] There have been several publications showing that prevalence of PH in CMPD ranges from 13% to 48% (Table 1), but exact prevalence is unknown.[8-16] Two factors may account for this wide range.

The first is the different diagnostic methods used for PH diagnosis. The largest report on the association of PH and CMPD is from Dingli et al. Diagnosis codes were utilized to identify patients with both CMPD and PH. PH was defined as right ventricular systolic pressure (RVSP) >35 mm Hg on Doppler transthoracic echocardiography (TTE) or mPAP >25 mm Hg on RHC or pulmonary angiography.[16] Because of the search strategy utilized, a prevalence rate could not be calculated, but the authors found that 26 patients met inclusion criteria (CMPD plus PH unexplained by other medical conditions). They concluded that given the rarity of idiopathic pulmonary arterial hypertension (PAH) in the general population (expected to see <1 case of idiopathic PAH in their entire CMPD cohort), the 2 diseases were likely related. Of the 26 patients in their cohort, 22 (92%) received treatment for CMPDs, which included therapy with hydroxyurea, anagrelide, or busulfan. PH was diagnosed a median of 8 years after recognition of the CMPD.

In a subsequent prospective study, Chebrek and coworkers evaluated 103

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Table 1. Prevalence of PH in CMPDs

Author	Year	n	Diagnosis	PH Definition	Prevalence %
Reisner et al[8]	1992	30	Echo	RVSP >35 mm Hg	13%
Garcia-Manero et al[14]	1999	6	Echo (6/6) RHC (4/6)	RSVP >35 mm Hg mPAP >25 mm Hg	Unknown
Dingli et al[16]	2001	26	Echo (26/26) RHC (5/26)	RSVP >35 mm Hg mPAP >25 mm Hg	Unknown
Garypidou et al[9]	2004	24	Echo	RVSP >35 mm Hg	41.7%
Gupta et al[11]	2006	25	Echo	RVSP >35 mm Hg	48%
Altintas et al[10]	2007	46	Echo	RVSP >35 mm Hg	47.8%
Cortelezzi et al[12]	2008	36	Echo	RVSP ≥35 mm Hg	36%
Guilpain et al[13]	2008	10	RHC	mPAP >25 mm Hg and Pulmonary capillary wedge pressure <15 mm Hg	Unknown
Chebrek et al[15]	2014	103	Echo	RVSP >35 mm Hg	<5%
Adir et al[19]	2015	49	Echo	RVSP >35 mm Hg	18.4%

consecutive patients with CMPDs for the presence of PH, defined as an RVSP >35 mm Hg by echocardiography. Five patients were found to have an unexplained elevation in pulmonary artery (PA) pressure (<5%),[15] and another 3 patients were found to have elevated pulmonary pressures in association with a known cause (left heart disease and/or chronic pulmonary embolism [PE]). Finally, Gupta et al reported one of the highest prevalences of PH, with 52% (14/27) of patients with CMPD having elevated PA pressures by echocardiogram.[11] Two patients had a reduced left ventricular ejection fraction and were excluded from further analysis; the remaining patients had no other known risk factor for PH. Among these 12 patients, 7 had essential thrombocytosis (ET) and 5 had polycythemia vera (PV). Diagnosis of PH was based on measurements obtained by TTE with Doppler study and was established if RVSP was estimated >35 mm Hg.

Given that PH in the majority of patients in these studies was diagnosed based on Doppler TTE and not confirmed by RHC, the rate of PH may be inaccurate. Alternatively, because clinical signs of PH appear at advanced stages of the disease and chronic hypoxemia can confound the diagnosis of CMPD, the prevalence of PH may also be underestimated. Either way, the lack of a uniform diagnostic method appears to be one factor that leads to a wide range in incidence.

The second factor likely contributing to the variable prevalence rate is that CMPD is not a single entity, but rather includes a spectrum of disorders. Higher rates of PH may be seen in one disorder when compared to another, changing the overall incidence in a cohort, which includes all CMPDs. For example, Altintas and colleagues reported a diagnosis of PH in 22/46 patients (47.8%) with essential thrombocytosis.[10] Dingli et al and Tefferi report that among CMPDs, myelofibrosis with myeloid metaplasia (MMM) appears to be most frequently associated with PH.[16,17]

PATHOGENESIS

Three distinct forms of PH associated with CMPD (PH-CMPD) have been identified: chronic thromboembolic pulmonary hypertension (CTEPH), which is often diagnosed at an early stage of CMPD; precapillary PH mimicking PAH, often occurring later in the course of CMPD; and drug-induced-PH.[18,19] Guilpain et al, in their case series of 6 patients, describes the differing time course of CTEPH vs PAH-like conditions. In this series, all 6 cases of CTEPH were made at the same time as the diagnosis of MPDs, and the authors concluded that CTEPH could be the first manifestation of the MPD, particularly for PV. In contrast, for the 4 patients with precapillary PH mimicking PAH, Guilpain et al found that PH developed later in the course of the disease, with a median of 162 months (range: 120-140) after the diagnosis of CMPD.[13] Similarly, Dingli et al found that precapillary PH was diagnosed a mean of 8 years after recognition of the MPD.[16]

The mechanism of development of CTEPH in CMPD is multifactorial. In PV and in ET, it is characterized by thrombophilic states that can lead to microcirculatory disturbances and subsequent arterial and venous thrombosis. Marvin and Spellberg have also suggested that thrombocytosis may cause PH mediated by pulmonary capillary obstruction due to cellular components, involving platelet aggregation, microthrombosis, stasis, and vasoconstrictor effects.[20] Additionally, high hematocrit values seen in PV lead to blood hyperviscosity, which increases risk for thrombosis.[21,22] Specifically, JAK-2 mutations in PV predisposes to polymorphonuclear cell activation, platelet aggregation and activation, and subsequent development of thrombosis.[23]

Precapillary PH mimicking PAH also has several pathogenic mechanisms, including portal hypertension, cytotoxic chemotherapies, megakaryocyte embolism, and enhanced angiogenesis.[13] Portal hypertension is a well-known complication of myeloid metaplasia and myelofibrosis, which can lead to PAH.[17,26] Cytotoxic chemotherapy may result in pulmonary damage or promote pulmonary veno-occlusive disease.[25] Megakaryocyte embolism of pulmonary vessels may be caused by translocation of megakaryocytes from the bone marrow, spleen, or liver to the lungs, in patients with progressive myeloproliferative syndrome, finally leading to PH. In addition, they secrete vasoactive cytokines, which propagate the development of PH.[26] Finally, a possible pathogenic

link between CMPDs and PH has been found in the peripheral blood and bone marrow, because of an enhanced angiogenesis. In that study, patients with primary myelofibrosis and PH had higher bone marrow microvessel density and vascular endothelial growth factor levels, suggesting the presence of a pro-angiogenic phenomenon.[12]

More recently, pathologic mechanisms for development of PH have been described in relationship to medications used for treatment of CMPD for both dasatinib and anagrelide. In the largest case series published to date, dasatinib, a tyrosine kinase inhibitor, was noted to cause incident PH in 9 patients reported in the French PH registry between November 2006 and September 2010. Clinical, functional, or hemodynamic improvements were observed within 4 months of dasatinib discontinuation in all but 1 patient. The authors concluded that dasatinib may induce severe precapillary PH, fulfilling the criteria of PAH, thus suggesting a direct and specific effect of dasatinib on pulmonary vessels.[27] This is supported by work published by Nagaraj and coworkers, who demonstrated that tyrosine kinase is crucial for potassium channel function in human pulmonary arteries. Under physiological conditions, a low pulmonary vascular tone is maintained by Src family tyrosine kinase (SrcTK), and that inhibition of SrcTK will lead to vasoconstriction of pulmonary resistance arteries and thus to an increase in PA pressure.[29] The concern over dasatinib leading to drug- and toxin-induced PAH is reflected in the updated PH guidelines from the 2013 WSPH, which now include dasatinib in the list of drugs that can result in PAH (Group 1.3 of the WSPH).

Anagrelide is an oral imidazoquinazoline agent with an anticyclic adenosine monophosphate (AMP) phosphodiesterase activity, and inhibits platelet aggregation in both humans and animals. It has been shown to have potent platelet-reducing activity in ET and related disorders. The introduction of anagrelide was suggested to be, at least in part, involved in the pathogenesis of biopsy proven pulmonary veno-occlusive disease (PVOD) in a 66-year-old female with myelodysplastic syndrome (MDS).[30] Overall, there is less literature to support a relationship between anagrelide and PH. Dingli and coworkers reported that 7 of 26 patients with PH were exposed to anagrelide, but only 3 of them had received it prior to their diagnosis of PH.[16]

DIAGNOSIS

Clinical Presentation

The symptoms exhibited by patients with PH-CMPD are related to both PH and the underlying disease process. PH symptoms are related to progression of underlying right ventricular (RV) dysfunction and commonly include shortness of breath, fatigue, weakness, angina, and syncope. Abdominal distention and ankle edema also develop with progressive RV failure.[31] In an Internet survey of 1179 patients with CMPD, frequency of self-reported symptoms included fatigue, pruritis, night sweats, bone pain, fever, and weight loss.[34]

The physical examination findings of PH manifest themselves late in the disease process and include: left parasternal lift, an accentuated pulmonary component of the second heart sound, an RV third heart sound, a pansystolic murmur of tricuspid regurgitation, and a diastolic murmur of pulmonary regurgitation. Elevated jugular venous pressure, hepatomegaly, ascites, peripheral edema, and cool extremities characterize patients with advanced disease. Wheezing and crackles are usually absent.[31] Other physical examination signs relate to the CMPD itself and include hepatomegaly, splenomegaly, conjunctival injection, facial plethora, skin excoriations, and gouty arthritis and tophi.[34]

Imaging

The following chest imaging modalities are typically performed during a workup on patients suspected of having PH and CMPD:

- Chest radiography (CXR) may reveal cardiomegaly and enlargement of the pulmonary arteries. Although these findings may indicate the presence of PH, they are nonspecific, and normal radiographic findings do not rule out PH.[35]
- A ventilation/perfusion (V/Q) lung scan should be performed in patients with PH to look for CTEPH. The V/Q scan has been the screening method of choice for CTEPH because of its higher sensitivity compared with computed tomography pulmonary angiography (CTPA), especially in experienced centers. A normal or low-probability V/Q scan effectively excludes CTEPH with a sensitivity of 90% to 100% and a specificity of 94% to 100%.[32]

Pulmonary Function Tests and Arterial Blood Gas Analysis

There are currently no established patterns on pulmonary function testing (PFT) in patients with CMPD. A case series of 12 patients with PV by Greening et al noted a significantly raised single-breath diffusion capacity (mean 152% predicted +/− 14%) that remained so even after correction for hemoglobin (mean 139% +/− 13%), perhaps due to elevated red cell volume.[36] For the subgroup with CMPD and CTEPH, a mild to moderate restrictive defect may be detected in approximately 20% of patients. In addition, a modest reduction in single-breath diffusing capacity for carbon monoxide (DLCO) may be present, though a normal value does not exclude the diagnosis. Furthermore, CTEPH patients will frequently exhibit some degree of hypoxemia, and if measured, elevated dead-space ventilation, both worsening with exercise.[47]

Electrocardiogram

An electrocardiogram (ECG) may provide supportive evidence of PH, but a normal ECG does not exclude the diagnosis. An abnormal ECG typically occurs in severe rather than mild PH and may include: P pulmonale, right axis deviation, RV hypertrophy, RV strain, right bundle branch block, and QTc prolongation. Supraventricular arrhythmias may occur in advanced disease, in particular atrial fibrillation and flutter.[31]

Echocardiogram

Transthoracic echocardiography is the standard noninvasive method of screening for PH. It is also useful to assess RV function and detect potential

cardiac causes of PH. Indications for echocardiography in patients with CMPD include: screening for PH, evaluation of concomitant left heart disease, and selection of patients for RHC. A peak tricuspid velocity of 2.9–3.4 m/s in the presence of echocardiographic signs suggesting PH such as RV dilation, enlarged PA diameter, increased right atrial area, and respiratory variation in diameter of the inferior vena cava or peak tricuspid velocity of >3.4 m/s alone[31] indicates a high probability of PH.

RHC and Vasoreactivity

The fifth WSPH defines PAH as mPAP ≥25 mm Hg plus pulmonary artery wedge pressure (PAWP) ≤15 mm Hg and pulmonary vascular resistance (PVR) >3 Wood units by RHC. Pulmonary vasoreactivity is recommended for patients with idiopathic PH, heritable PH, and drug-induced PH. In all other forms of PAH and PH, the results can be misleading and responders are rare.[31] At this time, RHC is not routinely recommended in all patients with CMPD, but is the gold standard for assessment of PH-CMPD. No differences in hemodynamic characteristics have been observed between CTEPH and PAH forms of PH-CMPD.[13] When PH is present in patients with CPMD, moderate to severe elevation in PA pressures may be present. A retrospective case series by Guilpain et al documented an average mPAP of 53 mm Hg (range 36-59) in 4 of 10 patients with CMPD.[13]

CLINICAL IMPLICATIONS

The clinical implications for CMPD patients that develop PH are quite severe. Specifically, it has been demonstrated that once a CMPD patient exhibits clinically significant PH, the patient's life expectancy is shortened. Dingli et al reported on a cohort of 26 patients in which there were 21 deaths with the median survival time after PH diagnosis of 18 months. Neither antiplatelet agents nor cytoreductive therapies were shown to delay the progression of PH, and the majority of deaths were a result of a cardiopulmonary cause.[16]

Additionally, Garcia-Manero et al found that the interval between the development of dyspnea (leading to the diagnosis of PH) and death was <7 months in 5 out of 6 patients.[14] Precapillary PH (PAH-like) also generally occurs late in the course of CMPD, and the more advanced underlying disease may also contribute to the poor prognosis. In contrast, for patients with CTEPH who are amenable to pulmonary thromboendarterectomy, there may be reversal of PH and improved prognosis.[19] Spontaneous improvement of severe PAH in CMPD after withdrawal of dasatinib has been described in several isolated case reports and case series.[41-45] Montani and colleagues reported that hemodynamics improved after dasatinib withdrawal in 7 of 8 patients, but no patient demonstrated complete normalization of pulmonary hemodynamic indices.[28] The role for PAH therapies remains unclear; Groeneveldt et al reported that PAH-specific therapies were not effective in dasatinib-associated PAH,[36] while in the series by Montani et al, PAH-specific therapy was attempted in 2 patients simultaneous with dasatinib withdrawal, making assessment of efficacy difficult.[27]

MANAGEMENT

There is little guidance regarding the appropriate management of the 3 distinct forms of PH associated with CMPD. Currently, no data specific to CTEPH associated with CMPD are available. However, pulmonary endarterectomy is the first choice treatment in patients with WHO Group 4, CTEPH. In CTEPH patients with inoperable disease, medical therapy including diuretics, anticoagulants, and PAH-specific therapy should be considered.[19]

For example, the 2008 BENEFiT trial randomized 157 patients with inoperable CTEPH or recurrent PH after endarterectomy to receive placebo or bosentan, an endothelial receptor antagonist. Bosentan demonstrated a statistically significant positive treatment effect on hemodynamics. However, no improvements were observed in exercise capacity.[37] Among patients with technically inoperable CTEPH, riociguat, a soluble guanylate cyclase stimulator, was shown to improve exercise capacity, PVR, WHO functional class, and levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with inoperable CTEPH or recurrent PH after pulmonary endarterectomy,[38] and riociguat has been approved by the US Food and Drug Administration (FDA) for this indication. Unfortunately, there are no specific studies to address CTEPH specifically associated with CMPD. An additional challenge is that the currently approved pharmacological therapies for PAH do not have a specific indication for Group 5 disease states.

Clinical trial data to support routine use of pulmonary vasodilators in precapillary PH associated with CMPD are also lacking, including endothelin receptor antagonists, prostacyclin analogues, or phosphodiesterase-type 5 inhibitors. Whether treatment of the underlying disease is beneficial also remains unclear. For example, Tabarroki et al described 15 patients with myelofibrosis and PH treated with ruxolitinib, and in 66% of the patients, an improvement of PA pressure and RV function measured by echocardiography was observed.[39] In contrast, a recent case report by Low and coworkers detailed an association between worsening PAH and ruxolitinib, with improvement on withdrawal of the drug on 2 separate occasions in a 57-year-old woman with progressive myelofibrosis.[40] Further data would be required to support the use of any current FDA-approved PAH-specific therapy or CMPD-specific therapy for the purpose of treating PH associated with CMPD.

CONCLUSION

Three distinct clinical forms of PH-CMPD have been described: CTEPH, precapillary PH, and drug-induced PAH; however, the exact incidence and prevalence in CMPDs is poorly defined. Nonetheless, new-onset or progressively increasing dyspnea in a patient with CMPD should prompt clinicians to investigate for PH. A definitive diagnosis of PH associated with CMPD must include an RHC. Unfortunately, when PH is present it portends a poor prognosis and is associated with an increased risk of mortality, and as of yet, data about the current use of specific PAH therapies in this group of patients

are still not available. Therefore, clinical judgment must be employed to successfully manage patients with PH-CMPD.

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