

Incidence of Pulmonary Hypertension in Patients with Chronic Myeloproliferative Disorders

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Study Objective: To assess the incidence of pulmonary hypertension (PH) in patients with chronic myeloproliferative disorders (CMPD).

Method: Twenty-seven patients with a diagnosis of CMPD were included in the study. Patients were excluded if they had a secondary cause of PH. Diagnosis of PH was established if right ventricular systolic pressure (RVSP) by transthoracic echocardiography (TTE) was >35 mmHg.

Results: Diagnosis of PH was established in 14 out of 27 patients. Two patients were excluded from analysis because of poor ejection fraction on TTE, resulting in a final diagnosis of PH in 12 of 25 (48%) patients. Of these 25 patients, seven of nine with essential thrombocytosis (ET), five of 14 with polycythemia vera (PV), and 0 out of two with chronic myeloid leukemia (CML) had PH. All patients were asymptomatic at the time of their most recent visit. There was no relationship between PH and age at diagnosis, duration of disease, platelet count and hematocrit at diagnosis or during follow-up, both for the entire cohort or for specific diagnosis of ET or PV.

Conclusion: Pulmonary hypertension appears to be common in patients with CMPD. Further studies are needed to evaluate the impact of treatment on PH and long-term survival in these patients.

Key words: chronic myeloproliferative disease ■ pulmonary hypertension ■ essential thrombocytosis ■ polycythemia vera ■ chronic myeloid leukemia

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BACKGROUND

Increased incidence of pulmonary hypertension (PH) has been reported in patients with chronic myeloproliferative disorders (CMPD).¹⁻⁷ The exact incidence,

however, is unknown. Most of the reported literature consists of case reports or small retrospective studies. A recently published prospective study of PH in CMPD included 24 patients, and the majority of them had essential thrombocytosis.⁵ We conducted a prospective study at Coney Island Hospital to assess the incidence of PH in our patients with CMPD.

MATERIALS AND METHODS

All patients being followed at Coney Island Hospital in the hematology clinic with a diagnosis of CMPD were eligible for the study. The diagnosis of CMPD was established by standard criterion.⁸⁻¹⁰ After a detailed history and examination, patients were excluded if they had any secondary cause of PH—for example, chronic obstructive lung disease, congestive heart failure or history of recurrent venous thromboembolism. Diagnosis of PH was based on measurements obtained by transthoracic echocardiogram (TTE) and Doppler study, all of which were done by one technician and read by a single cardiologist. PH was established if estimated right ventricular systolic pressure (RVSP) >35 mmHg.

The institutional review board in our institution approved the study. All patients signed an informed written consent to participate in the study.

Statistical differences in means of continuous variables between those with and without PH were assessed using independent t tests. Mean change in continuous variables over time was assessed using paired t tests. Alpha was set at $p < 0.05$.

RESULTS

Twenty-eight patients with diagnosis of CMPD were included in the study. One patient was excluded later because of failure to obtain an echocardiogram. Of the remaining 27 patients, nine had essential thrombocytosis, 15 had polycythemia vera and three had chronic myeloid leukemia (CML). Diagnosis of PH was established in 14 of the 27 patients by TTE. Two patients were excluded from analysis because of poor ejection fraction, one with polycythemia vera and one with CML, resulting in a final diagnosis of PH in 12 out of

25 patients (48%). Of these 25 patients, seven of nine with essential thrombocytosis, five of 14 with polycythemia vera and 0 of two with CML had PH. All the patients were asymptomatic at the time of their most recent visit within the last year.

Nine patients were male and 16 were female. Median age at diagnosis of the entire cohort was 59 years (mean 56.2 years, range 29–73 years). Mean age at diagnosis was not significantly different between those with PH (54.5 years) and those without PH (57.8 years), (p=0.54). Median duration of disease was six years (mean 8.8 years, range 1–20 years). Mean duration of disease was not significantly different between patients with PH (8.3 years) and without PH (9.2 years) (p=0.72). The clinical and laboratory data on all the patients at the time of diagnosis and follow-up are presented in Tables 1–3.

Mean platelet count at diagnosis was not significantly different in patients with PH (732 k/μL, SD 394 k/μL) and without PH (557 k/μL, SD 283 k/μL) (p=0.21). The difference in mean platelet count at follow-up for those with PH (419 k/μL, SD 144 k/μL) and those without PH (355 k/μL, SD 118 k/μL) (p=0.24) was not statistically significant. In the group as a whole, mean platelet counts dropped significantly from diagnosis (641 k/μL, SD 345 k/μL) to follow-up (385 k/μL, SD 132 k/μL) (p<0.001). The mean drop in platelet count in the group with PH (-313 k/μL, SD 351 k/μL) was similar to that in

the group without PH (-203 k/μL, SD 253 k/μL) (p=0.37).

Mean hematocrit at diagnosis in those with PH was 46.5%, SD 8.3% and in those without PH 53.5%, SD 10.2% (p=0.07). Mean hematocrit at follow-up was not significantly different for those with PH (39.4%, SD 4.6%) than for those without PH (40.8%, SD 5.0%) (p=0.50). In the group as a whole, mean hematocrit dropped significantly from diagnosis (50.1%, SD 9.8%) to follow-up (40.1%, SD 4.7%) (p<0.001). The mean drop in hematocrit of the group with PH was -7.0%, SD 6.4% compared to those without PH was -12.7%, SD 9.4% (p=0.09).

Because of erratic and variable duration of aspirin use by individual patients, we could not determine its significance. All except patient #5 received phlebotomy, hydroxyurea and anagrelide at different times during the course of their disease, and no correlation could be established between treatment and presence of PH.

DISCUSSION

We are presenting a cohort of 25 patients with CMPD who were evaluated for the presence or absence of PH. Our study includes nine patients with essential thrombocytosis, 14 patients with polycythemia vera and two patients with CML. We had no patient with myelofibrosis with myeloid metaplasia (MMM). Of these, seven of nine patients with essential thrombocy-

Table 1. Demographic data, diagnosis and treatment characteristics of the patients

Pt. No	Age (Years)	Sex	Year Diagnosed	Diagnosis	Treatment	Aspirin Use
1	62	F	2002	ET	AN	N
2	86	F	1992	ET	HU	Y
3	61	F	2004	ET	AN	Y
4	80	F	1991	ET	HU	Y
5	39	F	2003	ET	None	Y
6	54	F	2000	ET	AN	N
7	60	F	2002	ET	HU, AN	N
8	69	M	1991	ET	HU, AN	Y
9	79	F	1994	ET	HU, PL	Y
10	55	F	1991	PV	AN, HU	Y
11	56	F	1994	PV	HU, PL	Y
12	74	M	1999	PV	HU, PL	Y
13	47	F	2001	PV	HU, PL	Y
14	69	M	1999	PV	HU, PL	Y
15	65	M	1999	PV	PL	Y
16	62	M	1985	PV	HU, PL	Y
17	71	M	2001	PV	HU, PL	Y
18	88	F	1990	PV	HU, PL, AN	Y
19	65	F	1993	PV	HU, PL	N
20	65	F	1989	PV	HU, PL	Y
21	87	M	1990	PV	HU, PL	N
22	43	F	2003	PV	PL, AN	Y
23	85	M	1992	PV	HU, PH	Y
24	35	M	1999	CML	HU, GL	Y
25	66	F	2003	CML	GL	N

AN: anagrelide, HU: hydroxyurea, PL: phlebotomy, IFN: interferon, GL: gleevac, N: no, Y: yes

tosis and five out of 14 with polycythemia vera had PH by TTE and Doppler echocardiography. None of the two patients with CML had evidence of PH.

PH is well known in CMPD but most of the literature consists of case reports or small studies.^{1-5,7} A retrospective study was published in *Chest* in 2001, with a cohort of 26 patients who had both CMPD and PH.⁴ Of these 26 patients, five had essential thrombocytosis, six had polycythemia vera, one had CML, two had myelodysplasia and 12 had MMM. The authors found a relationship between elevated platelet count, hemoglobin level and presence of PH. A recent prospective study from Greece of 24 patients with CMPD by Garypidou et al.⁵ included two patients with polycythemia vera, 14 patients with essential thrombocytosis, six patients with MMM and two patients with CML. Unlike this study, we had a large cohort of polycythemia vera consisting of 14 patients. Whereas five out of 14 (36%) patients with polycythemia vera in our study had PH, neither of the two patients with polycythemia vera in the Garypidou et al.⁵ study had PH. The other findings in our study are similar to this study, in that age, sex, duration of disease, hematocrit and platelet count did not predict presence or absence of PH.

All the patients in our study were asymptomatic, and PH in most cases was mild. None of our patients needed treatment for PH. It is well known that symptoms of

mild PH are often subtle.¹¹ Since PH is usually diagnosed after symptoms develop, it is possible that most cases of mild, asymptomatic PH remain undiagnosed.

TTE is a good noninvasive method of diagnosing PH¹² and has the advantage of excluding cardiac causes of PH.

The most important question is whether this high incidence of PH in our study is truly secondary to CMPD. We believe that PH in these cases is secondary to CMPD due to many reasons. First of all, the incidence of primary PH in general population is very low (0.2 cases per 100,000) and usually occurs in the third or fourth decade.^{11,13} So the very high incidence of PH—48% in our study—is not by chance. We ruled out pulmonary embolism as a cause of PH by chart review of history and radiological studies but did not do baseline ventilation/perfusion scan or computed tomography (CT) scan of the chest as part of exclusion criteria since all our patients were asymptomatic. Also, we believe that even if our patients had small pulmonary embolism, its likely etiology will be the hypercoagulable state due to the underlying CMPD. Nevertheless, it is possible that small pulmonary embolism may have contributed to PH in some cases.

Pathogenesis of PH in CMPD is multifactorial. It has been correlated to platelets in many studies.^{2,3,7,14,16} Marvin and Spellberg found obstruction of pulmonary capil-

Table 2. Laboratory data and transthoracic echocardiogram (TTE) findings

Pt no	Diagnosis	Duration of Disease (Years)	Plt at Dx (k/ μ L)	Plt at FU (k/ μ L)	Hct at Dx (%)	Hct at FU (%)	RVSP (mmHg)
1	ET	3	715	392	38.7	33.6	46
2	ET	13	686	433	45.5	41.8	WNL
3	ET	1	645	637	33.3	35.7	35
4	ET	14	1377	394	49.8	35.4	46
5	ET	2	634	620	37.2	38.1	46
6	ET	5	766	520	37	37.6	36
7	ET	3	710	551	45.1	38.2	WNL
8	ET	14	1440	507	44.3	37.8	36
9	ET	11	567	350	47.5	38.9	76
10	PV	14	403	308	54.3	33.2	WNL
11	PV	12	706	284	53.8	45.9	WNL
12	PV	6	354	178	49.4	39.4	36
13	PV	4	562	416	65.4	45.8	WNL
14	PV	6	166	184	57.7	46.8	WNL
15	PV	6	263	291	54	51.4	45
16	PV	20	742	336	58.2	42.2	35
17	PV	4	1236	383	59.6	44.9	WNL
18	PV	15	631	456	51.8	37.1	WNL
19	PV	12	320	140	63.8	46.4	WNL
20	PV	16	215	271	56.4	42.2	36
21	PV	15	207	280	55.4	41.8	WNL
22	PV	2	1070	526	51.6	41	36
23	PV	13	376	400	69.1	35.6	WNL
24	CML	6	491	477	34.7	38.5	WNL
25	CML	2	750	298	39	33.9	WNL

Dx: diagnosis, FU: follow-up, Hct: hematocrit, Plt: platelet count; ET: essential thrombocytosis; PV: polycythemia vera

Table 3. Results of different parameters in patients with and without pulmonary hypertension

	n	Age at Dx (Years)	Duration of Disease (Years)	Mean Plt at Dx (k/ μ L)	Mean Plt at FU (k/ μ L)	Mean Hct at Dx (%)	Mean Hct at FU (%)
PH+	12/25	54.5	8.3	732 \pm 394	419 \pm 144	46.5 \pm 8.3	39.4 \pm 4.6
PH-	13/25	57.8	9.2	557 \pm 283	355 \pm 118	53.5 \pm 10.2	41.8 \pm 5.0
p value				0.21	0.24	0.07	0.5

Dx: diagnosis, FU: follow-up, Hct: hematocrit, Plt: platelet count

larities by megakaryocyte leading to stasis and secondary microthrombosis in one patient with MMM and PH.⁷ Right heart failure resolved with the correction of thrombocytosis in this patient. Furthermore, autopsy studies¹⁵ have demonstrated the presence of atypical megakaryocytes and thrombotic material in the lung capillaries of patients with PH and CMPD. Other evidence implicating platelets in the pathogenesis of PH is the presence of increased level of thrombopoietin in pulmonary arteries of patients with PH.¹⁶ Significant local platelet activation, thromboxane A2 generation has also been demonstrated in patients with CMPD and PH.^{2,3}

In general, survival of patients with symptomatic PH is poor. Since our patients are asymptomatic, their prognosis may be better; however, the duration of follow-up after establishing the diagnosis of PH in our study is short (10–12 months).

Since PH appears to be common in patients with CMPD, more studies are needed to study the long-term impact of PH on survival in these patients. Impact of therapy, including platelet-lowering agents and aspirin, on development and progression of PH also needs to be studied.

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