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Case Report

Pulmonary Hypertension in a Patient with Essential Thrombocythemia

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A 67-year-old woman with essential thrombocythemia (ET) developed acute heart failure and marked pulmonary hypertension (PH). No clear cause for the PH could be initially found. We suspected that thrombocytosis might cause PH. Treatments with anticoagulant (heparin and warfarin), platelet-lowering (hydroxyurea), and antiplatelet (ticlopidine) agents resulted in improvement of the clinical, hemodynamic conditions, and the control of platelet counts. We found that the main etiology of PH in the present case might be the pulmonary capillary obstruction from local pulmonary microthrombosis complicated with ET. Although PH associated with ET is uncommon, it should be always considered as a possible cause of dyspnea in patients with ET.

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Introduction

Essential thrombocythemia (ET) is a chronic myeloproliferative disorder (CMPD) characterized by elevation of platelet count, which results from clonal proliferation of a single neoplastic multipotent stem cell, affecting primarily megakaryocyte production[1, 2]. ET is often associated with hemostatic complications, both thrombotic and hemorrhagic. Thromboembolic complications are the main cause of morbidity and mortality in ET, especially cerebral, myocardial, and peripheral arterial thrombosis[3, 4]. However, isolated pulmonary complications are infrequent in the CMPD. Thrombocytosis in the absence of thromboembolic disease has only rarely been suspected as the etiology of pulmonary hypertension (PH). Although the possible association of PH with CMPD has been suggested by some case reports and clinical studies[5-12], their etiology and treatment have been controversial. We report a case of severe PH developing coincidence with remarkable thrombocytosis. The PH might be possibly caused by local microthrombosis in pulmonary arteries (PA).

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Case Report

A 67-year-old woman was admitted to our hospital with complaint of exertional dyspnea (NYHA grade III). The dyspnea had been present for about one week, with the symptoms gradually worsening before admission. She had a history of hypertension of unknown duration. Seven years before current admission she had been diagnosed as ET, but she had no adequate therapy for ET since diagnosed. On physical examination, she was 150 cm tall and weighed 52 kg, the body temperature was 36.8℃, blood pressure was 140/108 mmHg with a regular pulse of 102 beats/min, and respiratory rate was 24 cycles/min. A grade 3/6 systolic murmur was heard at the left sternal border with the second intercostal space, but breathing sound was almost normal. There was edema of the face and upper and lower extremities. Arterial blood gas analysis showed PaO_2 44 mmHg, $PaCO_2$ 30.5 mmHg, pH 7.43 and HCO_3^- 20.6 mEq/l while breathing 14 liters O_2 through a facemask. Chest X-ray showed cardiomegaly (cardiothoracic ratio, 65%), enlargement of the proximal parts of PA bilaterally (Figure 1). An electrocardiogram revealed regular sinus rhythm at a rate of 105 beats/min, right axis deviation, clockwise rotation (with deep S wave in leads V_5 and V_6), S wave in lead I, Q wave in lead III, and inverted T wave in leads III, V_1-V_4 (Figure 1). Transthoracic echocardiography revealed enlarged right ventricle (RV)

with flattening of the interventricular septum at end-diastole in parasternal short-axis view. Doppler echocardiography revealed severe regurgitation of the tricuspid valve and the estimated pressure gradient between RV and right atrium (RA) was 68.5 mmHg. M-mode parameters of left ventricle are summarized in Table 1.

Table 1. M-mode and Doppler Measurements by Echocardiagraphy

IVS (mm)	Day 1	Day 4	Day 24
PW (mm)	11.8	11.8	11.5
LVDd (mm)	35.7	41.9	43.4
LVDs (mm)	19.8	25.8	27.6
EDV (ml)	53.3	74	82
ESV (ml)	12.4	17	21
SV (ml)	40	56	61
EF (%)	77	77	75
RV-RA PG (mmHg)	68.5	47.7	19.2

IVS=interventricular septum. PW=left ventricular posterior wall. LVDd=left ventricular end-diastolic dimension. LVDs=left ventricular end-systolic dimension. LVEDV=left ventricular end-diastolic volume. LVESV=left ventricular end-systolic volume. SV=stroke volume. LVEF=left ventricular ejection fraction (by Teichholz method). FS=fractional shortening. RV-RA PG=pressure gradient between right ventricle and right atrium.

Laboratory findings are summarized in Table 2. There were leukocytosis and remarkable thrombocytosis. Biochemical findings included slightly increased lactate dehydrogenase (LDH) and C-reactive protein (CRP) levels. Coagulation and fibrinolysis tests showed high levels of fibrin degeneration products (FDP) and D-dimer, and low prothrombin time (PT) and low levels of antithrombin-III (AT-III). Whereas, the other data, such as activated partial thromboplastin time (APTT), fibrinogen, protein C and protein S, were within normal limits. Both anti-cardiolipin antibodies and lupus anticoagulant were negative.

Based on these findings, we initially suspected acute pulmonary thromboembolism (APTE) as a cause of dyspnea, and performed further examinations. A chest enhanced computed tomography (CT) revealed enlargement of RA, RV, and proximal part of PA without definite signs of thrombi in PA. In addition, chest CT revealed mild pericardial and pleural effusion, and mild congestion in the bilateral lung fields. Enhanced CT of abdomen, pelvis, and lower extremities were also performed, which revealed no signs of venous thrombosis. Lung perfusion scintigram revealed some defects in the right upper and left lower lung fields (Figure 2). Pulmonary angiography (PAG) showed small filling defects in segmental branches of the right superior and left inferior PA (Figure 3). Right heart catheterization revealed highly elevated pulmonary arterial pressure (PAP; systolic/diastolic/mean: 81/32/52 mmHg) (Table 3).

Table 2. Laboratory Findings on Admission

Hematology	
RBC	400×10^4 /mm^3
Hgb	13.1 g/dl
Hct	38.9 %
WBC	10900 / mm^3
Plt	102×10^4 / mm^3
Blood Chemistry	
TP	7.3 g/dl
T-Bil	0.95 mg/dl
GOT	20 U/l
GPT	20 U/l
LDH	261 U/l
CPK	73 mU/dl
T.chol	172 mg/dl
TG	50 mg/dl
BUN	12.2 mg/dl
Cr	0.64 mg/dl
Na	140 mEq/l
K	3.7 mEq/l
Cl	107 mEq/l
Coagulation and Fibrinolysis tests	
Fibrinogen	396 mg/dl
PT	57.7 %
APTT	31.4 sec
FDP	25.6 μg/ml
AT III	70 %
D dimmer	17.6 μg/ml
Serological tests	
CRP	2.80 mg/dl

Symptomatic treatment for right sided heart failure due to PH was instituted with diuretics, and the dose of diuretics was increased because chest CT revealed mild increment of pericardial and pleural effusion on the 7th days after admission. Suspecting the possibility of APTE, intravenous urokinase (24×10^4 U/day for 7 days) and heparin (10,000 U/day) therapy were commenced from the day of admission. APTT remained

Table 3. Right Heart Catheterization

	Day 1	Day 7	Day 36
mRAP (mmHg)	9	2	1
RVP (mmHg)	81/1	52/-2	35/-2
RVEDP (mmHg)	16	6	4
PAP (mmHg)	81/32	55/20	36/15
mPAP (mmHg)	52	31	23
mPCWP (mmHg)	8	14	1
Cardiac Output (L/min)		4.45	4.31
Cardiac Index (L/min/m^2)		2.92	2.89

mRAP=mean right atrial pressure. RVP=right ventricular pressure. RVEDP=right ventricular end-diastolic pressure. PAP=pulmonary arterial pressure. mPAP=mean PAP. mPCWP=mean pulmonary capillary wedged pressure.

within normal limits despite increment of heparin (10,000 to 20,000 U/day), which seemed to be due to low AT-III. Accordingly, we commenced intravenous administration of AT-III (2,000 U/day for 3 days). Heparin was replaced with warfarin from 7 days after admission at a dose of 3.5 to 4.0 mg/day, which was adjusted to maintain an international normalized ratio (INR) of 1.5 to 2.5.

Platelet counts gradually increased from 102×10^4/mm^3 on admission to a maximum of 151×10^4/mm^3 on the 21st day after admission (Figure 4). Platelet function tests of peripheral venous blood were performed in vitro, which demonstrated normal platelet aggregation in response to ADP and collagen, and normal platelet activation in expression of p-selectin (CD62) on the platelet surface. Bone marrow aspiration showed hypermegakaryocytosis with normocellularity but no signs of malignancy. We diagnosed this patient as ET according to the criteria of Polycythemia Vera Study Group (PVSG)[13]. To reduce the platelet count, ranimustine was administered intravenously at a dose of 100 mg/day on 8th and 15th days after admission. In addition, oral administration of hydroxyurea was commenced at a dose of 1000 mg/day from 21st day after admission, and the dose was adjusted based on platelet count. Finally, ticlopidine (100mg twice per day) was combined with warfarin and hydroxyurea.

The patient subsequently had a good response to these treatments with fall in her platelets counts, clinical improvement in right heart failure, and decrement in PAP to 55/20 (mean 31) mmHg and 36/15 (mean 23) mmHg on 7th and 36th days after admission (Table 3). PAG showed no clear filling defects on 36th days after admission (Figure 3). However, lung perfusion scintigram revealed persistence of slight defects on 29th day after admission (Figure 2). Furthermore, hypoxemia (PaO_2 60 mmHg and $PaCO_2$ 37.6 mmHg; room air) persisted without complaint of dyspnea.

After discharge from the hospital, the patient had no evidence of right heart failure, and her oxygen saturation was improving and she was almost asymptomatic. The platelet count was kept within normal limits.

Discussion

In the present case, we found that the main predisposing factor for pulmonary thrombosis was ET, because our patient had no corroborating clinical history and clear radiological findings indicating deep venous thrombi as an origin of pulmonary thrombosis. In addition, our patient had no other predisposing factors for venous thrombosis, such as collagen diseases, nephrotic syndrome, diabetes mellitus, malignant diseases, or the use of oral contraceptive agents.

The possible association of PH with CMPD, such as ET, polycythemia vera, and myelofibrosis with myeloid metaplasia, has been suggested by some case reports and clinical studies[5~12]. Reisner et al reported that PH was demonstrated in 13% of patients with CMPD by Doppler echocardiography[6]. With regard to the etiology of PH, CMPD can elevate PAP by various potential mechanisms. It is generally accepted that megakaryocytes (10 to 150 μ) continually migrate from the bone marrow and are trapped within the pulmonary capillaries (7 to 10 μ in diameter) where transformation to platelets normally occurs[14]. Megakaryocytes have been demonstrated to be plentiful in the pulmonary capillary bed[15]. Marvin et al postulated the direct pulmonary capillary obstruction by megakaryocytes with stasis and secondary microthrombosis[7]. On the other hand, some previous studies have demonstrated the local pulmonary platelet activation and the increased metabolism of prothrombin and fibrinogen in patients with ET[7, 16]. In addition, it has been reported that platelet-derived growth factor released from activated platelets is a strong stimulus for smooth muscle hyperplasia[17]. By these mechanisms, ET can possibly introduce microthrombosis in the pulmonary circulation and elevate PAP.

We speculate that the following mechanisms of PH can be possibly applied to the present case. Firstly, chronic silent pulmonary microthrombosis may have existed subclinically without apparent subjective symptoms in the past, and have already been organized in part. The present case may be not acute onset but rapid deterioration of subclinical PH. We suspect that this mechanism may lead to her tolerance for high level of hypoxemia and PH on admission without severe dyspnea and hemodynamical shock. Secondly, we suspect that not only pulmonary thrombosis but also mild volume overload, which was indicated by

mild increment of pericardial and pleural effusion and elevated pulmonary capillary wedged pressure could contribute to PH to some degree. Thirdly, we cannot completely deny a possibility that complicated pulmonary thromboembolism, which arose from unknown origin of venous thrombi, could contribute to PH in acute phase.

Recommended treatments for PH in patients with thrombocytosis have varied from report to report and have been controversial: anticoagulant, antiplatelet and/or platelet-lowering therapy have been shown to be beneficial[5, 7, 8, 10, 11, 12]. Our patient showed good responses to the combination of these treatments. However, there is a possibility that thrombolytic and anticoagulant therapy alone might be able to result in gradual fall in PAP even if not combined with antiplatelet and platelet-lowering therapy. This possibility is indicated by the finding that PAP decreased despite the further increase of platelet counts in acute phase. In addition, we speculate that the persistence of hypoxemia and slight defects in lung perfusion scintigram in chronic phase was probably due to residual organized microthrombi of peripheral PA, for which these treatments were not effective.

Except pulmonary thrombosis, our patient seemed not to have other major thrombotic complications such as stroke, myocardial infarction, and peripheral arterial thrombosis because she did not present subjective symptoms nor radiological findings to indicate these thrombotic complications. Although we could not perform coronary angiography because of patient's rejection, she did not demonstrate such findings to indicate myocardial infarction as the elevation of cardiac enzymes or the asynergy of left ventricular wall motion by echocardiography.

In conclusion, we reported a case of PH in a patient with ET. We suspected the chronic silent microthrombosis in local PA as etiology of PH. Treatments with anticoagulant, platelet-lowering, and antiplatelet agents were effective for controlling platelet counts and PAP. Although PH associated with ET is uncommon, it should be always considered as a possible cause of dyspnea in patients with ET.

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