Journal of Cardiology Cases 6 (2012) e75–e77

Contents lists available at www.sciencedirect.com

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Case Report

Effect of vasodilators in patient with pulmonary hypertension associated with hemolytic anemia

Akira Yoshida (MD)[a], Isamu Mizote (MD)[a], Yasushi Sakata (MD)[a], Tetsuo Maeda (MD)[b], Yuzuru Kanakura (MD)[b], Keiko Yamauchi-Takihara (MD)[a,*], Issei Komuro (MD, FJCC)[a]

[a] Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Osaka, Japan
[b] Department of Hematology and Oncology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

ARTICLE INFO

Article history:
Received 23 January 2012
Received in revised form 1 May 2012
Accepted 12 May 2012

Keywords:
Pulmonary arterial hypertension
Autoimmune hemolytic anemia
Phosphodiesterase-5
Nitric oxide

ABSTRACT

Pulmonary arterial hypertension (PAH) has been described to associate with hemolytic anemia in updated clinical classification of pulmonary hypertension. A 56-year-old woman, diagnosed with warm antibody autoimmune hemolytic anemia (AIHA), was treated with oral corticosteroids at the Department of Hematology, Osaka University Hospital for 30 years. Her AIHA worsened 3 months before the admission, and she was treated with rituximab and cyclosporine in combination with prednisolone. Soon after she left the hospital, she developed dyspnea on effort and leg edema, therefore she was re-admitted to the Department of Cardiovascular Medicine. Echocardiogram and cardiac catheterization demonstrated PAH associated with AIHA. She was treated with three types of vasodilatory agents, resulting in an improvement in pulmonary arterial pressure and pulmonary vascular resistance after 6 weeks. A few weeks after she left the hospital, her hemolytic anemia became in remission without intensifying AIHA therapy, and did not worsen for a year of follow-up. Although corticosteroids are the first-line treatment for AIHA, medications for PAH should be considered when the first-line therapy for AIHA failed to improve PAH.

Introduction

Pulmonary arterial hypertension (PAH) has been described to associate with hemolytic anemia, such as sickle cell disease, thalassemia, and paroxysmal nocturnal hemoglobinurea, in an updated clinical classification of pulmonary hypertension [1]. The prevalence of PAH among patients with hemolytic anemia is estimated as 10–40%, and there are several reports presenting poor prognosis of PAH associated with chronic hemolytic anemia [2–4]. Nevertheless, PAH associated with autoimmune hemolytic anemia (AIHA) is uncommon and the precise etiology is still unclear [5]. Here, we report a case of PAH associated with AIHA and its successful treatment with vasodilatory agents.

Case report

A 56-year-old woman had been diagnosed with warm antibody AIHA for 30 years and treated with oral corticosteroids at the Department of Hematology, Osaka University Hospital. She never had a durable remission off therapy, and repeated exacerbations and remissions. As shown in Fig. 1, she had been treated with rituximab and cyclosporine in combination with prednisolone for several years. During the past 30 years of observation, her hemoglobin (Hb) concentration had never been maintained over 12 g/dL even with chemotherapy and blood transfusion. Her AIHA worsened in April 2010, e.g. Hb decreased to 6.8 g/dL and lactate dehydrogenase (LDH) increased to1924 IU/L, therefore, prednisolone was increased from 5 mg to 10 mg daily and rituximab (375 mg/m^2, once a week) was started. Her AIHA responded well to these treatments and she was discharged after 6 weeks of hospitalization.

One month after she left the hospital, she felt exertional dyspnea associated with leg edema and abdominal discomfort. She was then admitted to the Department of Cardiology in July 2010. Physical examination demonstrated that blood pressure was 110/62 mmHg, pulse rate 78 beats/min, and arterial oxygen saturation was 99% with 2 L/min nasal O_2. Laboratory findings are summarized in Table 1. The direct and indirect Coombs' tests were 2+ and +, respectively. Serological tests for connective tissue disease were negative. Her chest radiography showed that cardiothoracic ratio was 54% without pulmonary congestion and her electrocardiography showed deep S wave in I, small Q in III, and inverted T in III and V_{1-5}, presenting right ventricular hypertrophy. Cardiac echocardiography showed D-shaped left ventricular cavity with fluttering of interventricular septum in systole, the estimated right ventricular systolic pressure (RVSP) was 63 mmHg and the left ventricular ejection fraction was 68%. Ultrasonography showed no evidence of deep venous thrombosis in her legs. Right heart

* Corresponding author at: Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka, 565-0871 Japan. Tel.: +81 6 6850 6012; fax: +81 6 6850 6040.
E-mail address: takihara@imed3.med.osaka-u.ac.jp (K. Yamauchi-Takihara).

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http://dx.doi.org/10.1016/j.jccase.2012.05.002

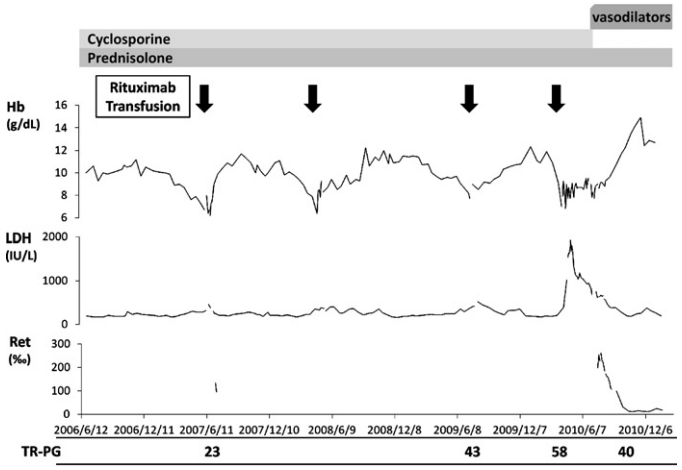

Fig. 1. Clinical course (i). Clinical course and treatment history of autoimmune hemolytic anemia (AIHA). Figure presents changes in hemoglobin (Hb), lactate dehydrogenase (LDH), reticulocyte (Ret), and tricuspid regurgitant pressure gradient (TR-PG) for recent 4 years.

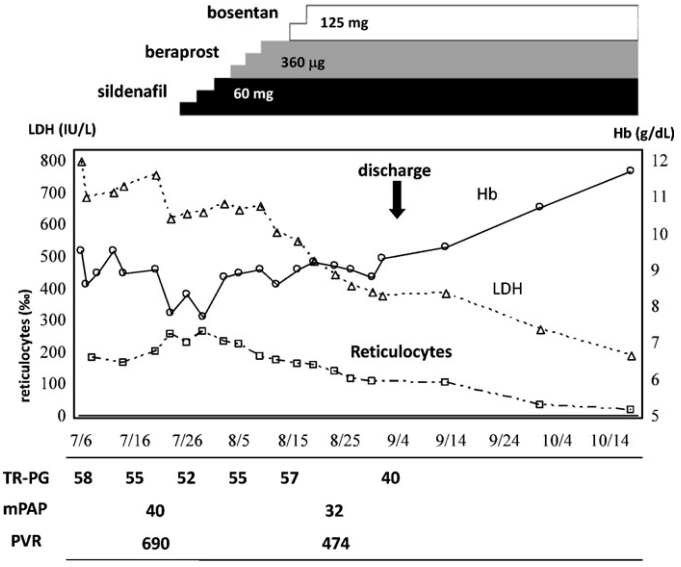

Fig. 2. Clinical course (ii). Sildenafil, beraprost, and bosentan were started sequentially from day 20 (2010/7/30). Sildenafil was started from 20 mg up to 60 mg, beraprost from 120 μg to 360 μg, and bosentan from 62.5 mg to 125 mg. Hb, hemoglobin; LDH, lactate dehydrogenase; TR-PG, tricuspid regurgitant pressure gradient; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance.

catheterization was performed on day 15, which revealed mean pulmonary artery pressure (mPAP) 40 mmHg, pulmonary capillary wedge pressure (PCWP) 9 mmHg, and pulmonary vascular resistance (PVR) 690 dyne s cm^{-5}, and she was diagnosed as having PAH.

Initially, her pulmonary hypertension was thought to develop in association with pulmonary thromboembolism because of various clinical features and lung perfusion scintigraphy, which showed segmental or sub-segmental defect. The contrast-enhanced computed tomography revealed no evidence of pulmonary thromboembolism. She was treated with diuretics and intravenous anticoagulants, and her symptoms of heart failure improved, however, RVSP was unchanged. Subsequently, she was diagnosed as having PAH presenting chronic thromboembolic pulmonary hypertension-pattern of perfusion scintigraphy which was developed in association with AIHA worsening, and we started to treat PAH by using specific medications: sildenafil, a phosphodiesterase-5 (PDE-5) inhibitor; beraprost, a prostacyclin analogue; and bosentan, an endothelin receptor antagonist. As shown in Fig. 2, these 3-types of vasodilatory agents were added sequentially. After a month of treatment, RVSP reduced to 45 mmHg and the right heart catheterization was repeated on day 50. The mPAP and the PVR significantly decreased to 32 mmHg and 474 dyne s cm^{-5}, respectively, indicating that PAH was markedly improved.

She left the hospital on day 59, thereafter her Hb gradually increased to 12 g/dL. Two months after the discharge, LDH and reticulocytes simultaneously decreased to normal range, suggesting that AIHA was improved without intensifying AIHA therapy (Fig. 2).

Table 1
Laboratory findings on admission.

WBC	6450/μL	C-reactive protein	0.15 mg/dL
RBC	230×10^4/μL	BNP	402.3 pg/mL
Hb	9.5 g/dL	Direct Coombs' test	2+
Hct	29.1%	Indirect Coombs' test	1+
MCV	126.3 Fl	Antinuclear antibody	(−)
MCHC	32.6%	Vitamin B12	836 pg/mL
Reticulocytes	17.8%	Folic acid	5.3 ng/mL
Platelet	36.2×10^4/μL	Haptoglobin	<2 mg/dL
LDH	796 IU/L	Blood gas analysis (2 L/min nasal O_2)	
Total bilirubin	2.8 mg/dL	pH	7.450
Indirect bilirubin	1.8 mg/dL	$PaCO_2$	33.6 Torr
AST	49 IU/L	PaO_2	84 Torr
ALT	16 IU/L	HCO_3^-	22.7 mmol/L
Na	146 mEq/L	Base excess	−0.6 mmol/L
K	4.0 mEq/L		
Cl	111 mEq/L	PT	42%
BUN	16 mg/dL	APTT	33 s
Creatinine	0.81 mg/dL	PT-INR	1.56
Uric acid	9.9 mg/dL	D-dimer	0.7 pg/mL
Creatine kinase	30 IU/L		

WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; LDH, lactate dehydrogenase; AST, aspartate-aminotransferase; ALT, alanine-aminotransferase; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; PT, prothrombin time; APTT, activated partial thromboplastin time; PT-INR, prothrombin time international normalized ratio.

Discussion

PAH is a syndrome of restricted blood flow associated with vasoconstriction, vascular remodeling, and thrombosis of small pulmonary arteries. PAH includes idiopathic and heritable PAH and associates with various conditions, such as connective tissue disease, human immunodeficiency virus infection, portal hypertension, and chronic hemolytic anemia [1]. To our knowledge, there are few reports of PAH associated with AIHA. Zhang et al. reported a case of PAH associated with AIHA as a first case in 2007. They reported that AIHA was successfully treated with corticosteroids, however PAH was unchanged [5]. AIHA is characterized by an increased breakdown of red blood cells (RBC) due to autoantibodies with or without complement activation. Binding with auto-antibody led to the sphering, increased osmotic fragility, and impaired deformability of RBC [6,7]. Therefore, mechanically damaged RBC may increase pulmonary vascular resistance. A recent report recognizes that hemolysis as an essential factor for the development of PAH [8].

It has been shown that cell-free Hb leads to nitric oxide depletion due to nitric oxide scavenging, dysregulation of arginine metabolism, and inhibition of endogenous nitric oxide synthesis. Consequently, nitric oxide depletion induces platelet activation, increases endothelin-1-mediated response, and enhances oxidative stress. All those events in turn develop pulmonary vascular remodeling, characterized by endothelial dysfunction, increased vascular tone, inflammation, and hypercoagulability, which ultimately result in pulmonary hypertension [9,10].

We treated PAH by using three different types of vasodilatory agents, prostacyclin analogue, endothelin receptor antagonist,

and PDE-5 inhibitor, which improved mPAP, PVR, and RVSP significantly, and subsequently Hb increased to 12 g/dL without transfusion and LDH decreased to normal range. During the past 30 years of observation, her Hb concentration had never exceeded 12 g/dL without transfusion.

Recently, L-arginine supplementation or PDE-5 inhibition was reported to improve hematologic and hemodynamic status in patients with sickle cell disease [11]. They suggest that augmentation of the cyclic nucleotide pathway by PDE-5 inhibition may improve hemodynamic and functional status in sickle cell disease. Although the precise mechanism for the improvement of anemia in this case is unknown, reduction in PVR and mechanical damage of RBC using vasodilatory agents might additionally attribute to prevent the hemolytic state.

In conclusion, we encountered a case of PAH associated with AIHA; her pulmonary hypertension was successfully treated with vasodilatory agents, and subsequently hemolytic anemia became in remission without intensifying AIHA therapy. Although corticosteroids are the first-line treatment for AIHA, treatment for pulmonary hypertension by specific agents should be considered when the first-line therapy for AIHA failed to improve PAH.

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