Official Case Reports Journal of the Asian Pacific Society of Respirology
Respirology Case Reports
OPEN ACCESS

Effectiveness of pulmonary vasodilators on pulmonary hypertension associated with POEMS syndrome

Kana Ohashi[1], Rintaro Nishimura[1], Shunsuke Sugimoto[1], Seiichiro Sakao[1], Nobuhiro Tanabe[1,2] & Koichiro Tatsumi[1]

[1]Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan.
[2]Department of Advanced Medicine in Pulmonary Hypertension, Graduate School of Medicine, Chiba University, Chiba, Japan.

Keywords
polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome, pulmonary hypertension (PH), macitentan, sildenafil, vascular endothelial growth factor (VEGF).

Correspondence
Kana Ohashi, Department of Respirology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana Chuou-ku, Chiba City, Chiba 260-8670, Japan.
E-mail: ohashi_kana0314@yahoo.co.jp

Received: 4 December 2018; Revised: 3 February 2019; Accepted: 5 February 2019.

***Respirology Case Reports*, 7 (4), 2019, e00411**

doi: 10.1002/rcr2.411

Abstract

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare plasma cell disease. Patients with POEMS syndrome are considered to be at a high risk of developing pulmonary hypertension (PH). We report a 51-year-old woman diagnosed with PH associated with POEMS syndrome. She was started on dexamethasone and thalidomide. Although, the plasma vascular endothelial growth factor (VEGF) level decreased, systolic pulmonary artery pressure (sPAP) remained high. Auto-peripheral blood stem cell transplantation improved the plasma VEGF and sPAP levels. Four years later, she presented with dyspnoea on exertion, and elevated plasma VEGF and sPAP levels. Subsequently, on administering sildenafil and macitentan, the plasma VEGF and PH levels improved. Pulmonary vasodilators can be considered when PH remains after treatment of POEMS syndrome.

Introduction

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare plasma cell disease. Plasma vascular endothelial growth factor (VEGF) levels are high in almost all patients, while pulmonary hypertension (PH) reportedly occurs in 33–48% of patients with POEMS syndrome [1]. However, the pathogenesis of PH associated with POEMS syndrome is not clear.

Although several studies have reported that PH associated with POEMS syndrome is reversible after successful treatment with steroids, thalidomide, or autologous stem cell transplantation [1–3], the reports of PH in POEMS syndrome treated with pulmonary vasodilators are limited [3].

Case Report

A 51-year-old female patient visited a hospital presenting with foot drop and paraesthesia, and was diagnosed with POEMS syndrome based on multiple mononeuropathy, monoclonal gammopathy, splenomegaly, thrombocytopenia, and membranoproliferative glomerulonephritis. One year later, the peripheral neuropathy worsened with plasma VEGF (normal range < 38.3 pg/dL) level increasing to 9950 pg/dL. Echocardiography indicated PH with an estimated systolic pulmonary artery pressure (sPAP) of 56 mmHg (Fig. 1) and normal left ventricular function.

The patient was started on dexamethasone and thalidomide. Consequently, plasma VEGF level decreased to 1290 pg/mL; however, sPAP level remained unchanged. Therefore, she received an auto-peripheral blood stem cell transplantation. Plasma VEGF level and sPAP decreased to 641 pg/mL and to 37 mmHg, respectively (Fig. 1).

Four years later, the patient complained of dyspnoea on exertion, along with plasma VEGF level increased to 904 pg/mL and sPAP increased to 90 mmHg. Because of no evidence of disease relapse except for elevated sPAP,

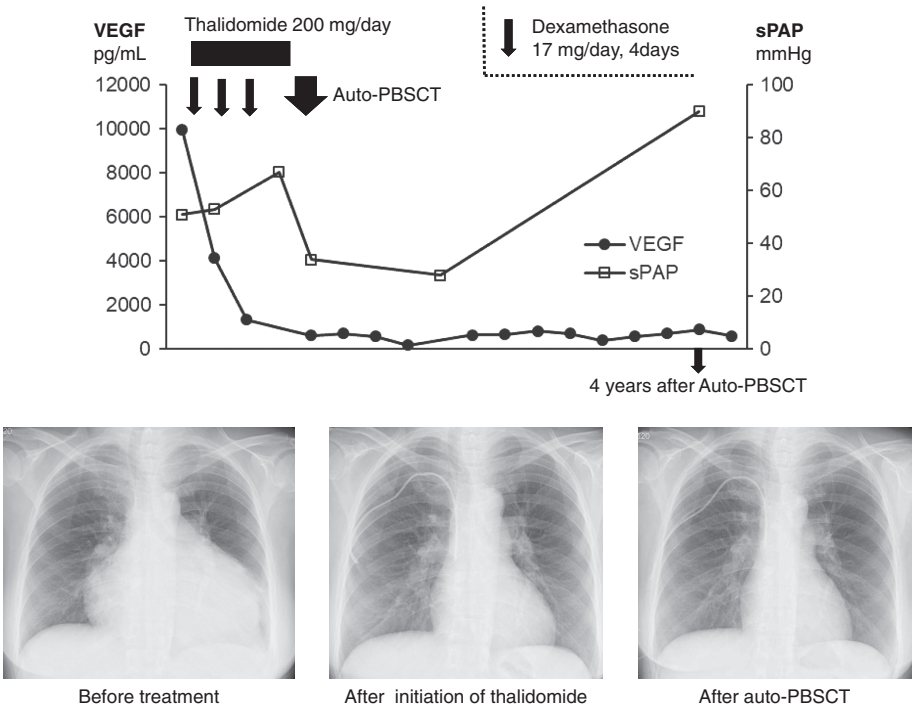


Figure 1. Clinical course of the patient before admission. PBSCT, peripheral blood stem cell transplantation; sPAP, systolic pulmonary artery pressure; VEGF, vascular endothelial growth factor.

she was referred and admitted to our department for evaluation and treatment of PH.

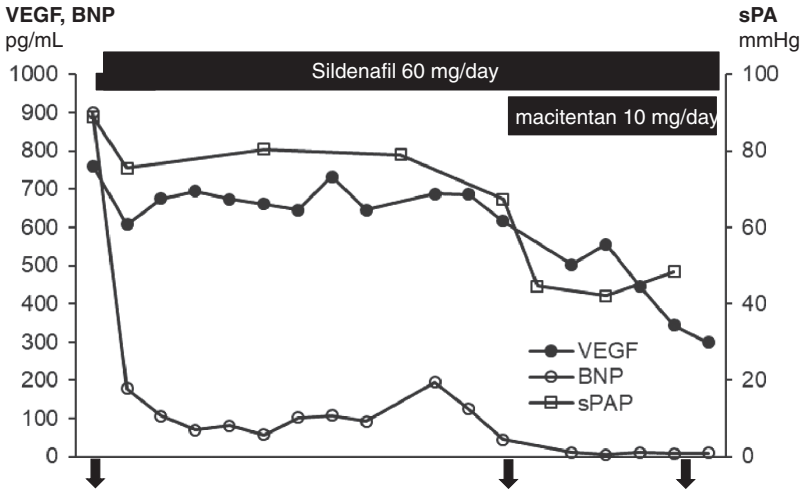
On admission, chest X-ray revealed prominent enlargement of the pulmonary arteries with a cardiothoracic ratio of 56%. No ventilation-perfusion mismatch was detected on a lung scintigraphic examination. Computed tomography demonstrated dilated pulmonary trunk and right ventricle. Hypertrophy of bronchovascular bundles with surrounding ground-glass opacity was slightly presented. Echocardiography demonstrated a normal left ventricular ejection fraction of 86.8% and sPAP of 81 mmHg. A pulmonary function test revealed mild obstructive ventilatory impairment with a decreased diffusion capacity of carbon monoxide (DLCO: 54.6%). The plasma VEGF and brain natriuretic peptide (BNP: normal range < 18.4 pg/dL) levels were 731 pg/mL and 901 pg/mL, respectively.

Right heart catheterization revealed an elevated pulmonary arterial pressure of 88/35 mmHg with a mean pulmonary artery pressure (mPAP) of 57 mmHg, a pulmonary arterial wedge pressure of 11 mmHg, a pulmonary vascular resistance (PVR) of 13.8 WU, and a cardiac index (CI) of 2.18 L/min/m^2. From these results, we concluded that the PH had worsened. Therefore, a PDE5 inhibitor, sildenafil, was started at 20 mg/day and the dose was increased to 60 mg/day, resulting in marked decrease of BNP level one month after initiation of treatment. Seventeen months after the initiation of sildenafil, the plasma VEGF and BNP levels decreased to 616 pg/mL and 65.5 pg/mL, respectively. The follow-up examination revealed improvement of PH (mPAP: 50 mmHg (98/27), PVR: 12.9 WU, and CI: 2.27 L/min/m^2). However, the mPAP remained high, thus, an endothelin receptor antagonist, macitentan (10 mg/day), was added. Seven months later, the plasma VEGF level improved to 555 pg/mL. World Health Organization functional class was improved from 3 to 2, and there was no finding of worsening in DLCO (60%) and renal function. Right heart catheterization revealed a more improved pulmonary haemodynamics than those before the initiation of macitentan (mPAP: 47 mmHg (86/20), PVR: 9.8 WU, and CI: 2.72 L/min/m^2) (Fig. 2).

Discussion

Here, we report for the first time on a patient diagnosed with POEMS syndrome with PH, who showed improvement of PH and VEGF level after combination therapy of vasodilators. Moreover, this case indicates heterogeneous mechanism of PH in POEMS syndrome.

POEMS syndrome is diagnosed with two mandatory major criteria, that is, polyneuropathy and clonal plasma cell disorder, one of three other major criteria, that is, Castleman's disease, sclerotic bone lesions, and plasma VEGF elevation, and one of the minor criteria, that is, organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, and thrombocytosis. Patients with POEMS syndrome have been reported to be at risk of



Right heart catheterization			
mPAP (mmHg)	57	50	47
PVR (W.U.)	13.8	12.9	9.8
CI (L/min/m^2)	2.18	2.27	2.72
PaO_2 (torr)	79.2	83	73
$PaCO_2$ (torr)	31.9	33.6	35.7
PvO_2 (torr)	29.5	29.5	37.6

Figure 2. Clinical course of the patient. Both plasma vascular endothelial growth factor (VEGF) and systolic pulmonary artery pressure (sPAP) levels decreased following administration of sildenafil and macitentan. BNP, brain natriuretic peptide; CI, cardiac index; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance.

developing PH; however, the precise mechanisms underlying PH are still unclear.

In our patient, the plasma VEGF level decreased because of treatments with steroid, thalidomide, and autologous stem cell transplantation. Moreover, the change of plasma VEGF level decreased in parallel to decreasing pulmonary arterial pressure although PH remained. Previous reports revealed elevated levels of pro-inflammatory cytokines, such as VEGF, tumour necrosis factor-α, and interleukin-6, in patients with POEMS syndrome and their positive correlation with disease progression. Furthermore, several reports have suggested the plasma VEGF level is closely related to the severity of PH in POEMS syndrome [1,2]. VEGF is a multifunctional cytokine that is associated with angiogenesis and vascular hyperpermeability. Therefore, increase of VEGF may cause enhancement of vascular hyperpermeability, endothelial proliferation and dysfunction, leading to vascular resistance. The postmortem examination of the lung of a patient with POEMS syndrome revealed pulmonary vascular remodelling, including plexiform lesions, which are consistent with pulmonary arterial hypertension (PAH) [4]. On the other hand, an autopsy study of another such patient revealed stenosis and occlusion of pulmonary arteries due to plasma cell infiltration, different from the histology of PAH [5]. These reports indicate that histological findings of PH associated with POEMS could be heterogeneous.

There is only one report of the effectiveness of sildenafil for PH associated with POEMS [3], but no report indicating the effect of combination vasodilator therapy. To treat PH associated with POEMS, our patient was started on sildenafil and macitentan. We observed that mPAP decreased concurrently with decreasing plasma VEGF level. Possibly, pulmonary arterial lesions seen in PAH were involved in pathogenesis of this case. On the other hand, decreases of sPAP and mPAP were modest compared to that in typical PAH patients. The indirect effect of vasodilators through VEGF suppression or heterogeneity of PH associated with POEMS may explain the treatment response.

In conclusion, we report the effectiveness of the vasodilators, sildenafil and macitentan, in a patient with PH associated with POEMS. Pulmonary arteriopathy seen in PAH may have occurred independently of underlying haematological condition. Pulmonary vasodilators can be considered when PH remains even after adequate treatment of POEMS syndrome.

Disclosure statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

References

1. Li J, Tian Z, Zheng HY, et al. 2013. Pulmonary hypertension in POEMS syndrome. Haematologica 98:393–398.
2. Niimi H, Arimura K, Jonosono M, et al. 2000. VEGF is causative for pulmonary hypertension in a patient with Crow-Fukase (POEMS) syndrome. Intern. Med. 39:1101–1104.
3. Shimomura Y, Hara M, Mizote I, et al. 2010. Sildenafil and steroid therapy effectively improved POEMS syndrome-associated pulmonary arterial hypertension. Int. J. Hematol. 92:774–776.
4. Czeczok T, Lin P, and Yi E. 2017. Plexogenic pulmonary hypertension associated with POEMS syndrome. Respir. Med. Case Rep. 22:168–170.
5. Chinen K, and Fujioka Y. 2012. Severe pulmonary hypertension caused by smoldering plasma cell myeloma: an autopsy case of POEMS syndrome. Case Rep. Med. 2012:836893.