ESC European Society of Cardiology

European Heart Journal - Case Reports (2018) **2**, 1–6
doi:10.1093/ehjcr/yty051

CASE REPORT

Reversal of pulmonary arterial hypertension in POEMS syndrome with thalidomide: a case report

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Received 28 December 2017; accepted 2 April 2018; online publish-ahead-of-print 27 April 2018

Introduction Pulmonary arterial hypertension (PAH) is a progressive and life-threatening disease characterized by the remodelling of distal pulmonary arteries in the absence of other cardiopulmonary disease, usually leading to right ventricular failure. Given the current European Society of Cardiology and the European Respiratory Society guidelines for the diagnosis and treatment of pulmonary hypertension (PH), most of the patients with severe PAH usually require to have a lifelong combination therapy that includes prostacyclin, phosphodiesterase-5 inhibitor, and endothelin receptor antagonist. However, the reversibility of PAH has been reported through the treatment of the underlying diseases or comorbidities.

Case presentation We present a case of a 45-year-old woman with a chief complaint of dyspnoea, eventually diagnosed with severe PAH in the setting of POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome that was successfully treated with thalidomide and dexamethasone.

Discussion Our case suggests that it would be important to consider associated syndromes when a diagnosis of PH is made, because treatment of the underlying condition may lead to improvement in PAH.

Keywords POEMS syndrome • Pulmonary arterial hypertension • Thalidomide • Case report

Learning points

- Early diagnosis and intervention with thalidomide and dexamethasone might contribute to a decrease of pulmonary vascular resistance, even in patients with severe pulmonary arterial hypertension (PAH) concomitant with POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome.
- It would be important to consider associated syndromes when a diagnosis of pulmonary hypertension is made, because treatment of the underlying condition may lead to improvement in PAH.

Introduction

Despite enormous efforts in research and the development of available therapies over the last two decades, pulmonary arterial hypertension (PAH) remains a progressive and relatively incurable disease.[1] Pulmonary arterial hypertension is a disease characterized by the remodelling of distal pulmonary arteries in the absence of other cardiopulmonary disease, usually leading to right heart failure and subsequent death without appropriate intervention.[2,3] Given the current European Society of Cardiology/European Respiratory Society guidelines for the diagnosis and treatment of pulmonary hypertension (PH),[4] most of the patients with severe PAH usually require to have a lifelong combination therapy that includes

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prostacyclin, phosphodiesterase-5 inhibitor, and endothelin receptor antagonist (ERA). However, the reversibility of PH has been reported through the treatment of the underlying diseases or comorbidities.[5–7] Here, we present a case of severe PAH concomitant with a syndrome of POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome that was successfully treated with thalidomide and dexamethasone.

Timeline

Time	Events
Initial presentation (Day 1)	Presented with 3-month history of shortness of breath
	Pulmonary hypertension (PH) diagnosed at clinic: based on symptom, history, blood work, chest X-ray, electrocardiogram, and transthoracic echocardiogram
1 month	Pulmonary arterial hypertension (PAH) concomitant with POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome diagnosed on admission
	Initiate tadalafil, 40 mg o.d., for PAH, but neither symptoms nor haemodynamic have been improved
3 months	Initiate thalidomide and dexamethasone for 5 cycles.
	(1 cycle: oral thalidomide, 200 mg o.d. from Days 1 to 28, and oral dexamethasone, 20 mg o.d. from Days 1 to 4)
Follow-up (1 year)	Significant improvement in symptomatic status (World Health Organization Class I) with no evidence of PAH on right heart catheterization. Tadalafil discontinued

Case presentation

A 45-year-old woman was referred to our institution with a 3-month history of shortness of breath on exertion. The patient did not have significant past medical history. On physical exam, she was noted to have a palpable lymph node in the neck and axilla; skin pigmentation around the neck, chest, and back; significant peripheral oedema of the lower limbs; and clubbed fingers on both hands were noted (*Figure 1*). Electrocardiogram showed right axis deviation, P pulmonale in lead II, V1R, and strain pattern in lead V1–3 (*Figure 2A*). Chest X-ray revealed significant cardiomegaly (*Figure 2B*). Pulmonary function test (PFT) was normal with the exception of impaired diffusing capacity of the lung for carbon monoxide (DLCO) at 30.4% (normal reference value: DLCO 80–120%) of predicted value. Transthoracic echocardiogram (TTE) revealed severe PH with an estimated pulmonary artery systolic pressure of 80–85 mmHg, significant right atrium (RA) and right ventricular (RV) enlargement, and RV impairment with a tricuspid annular plane systolic excursion (TAPSE) of 10.2 mm (normal reference value: TAPSE > 16 mm). Cardiac magnetic resonance (CMR) revealed mildly impaired RV function with right ventricular ejection fraction (RVEF) of 47% (normal reference value: RVEF 50–65%) (Supplementary material online). Moderate pericardial effusion was present (*Figure 3A, B*). Ventilation perfusion scan indicated a low probability of pulmonary thromboembolism. Contrast-enhanced computed tomography (CT) did reveal significant dilatation of RA, RV, and pulmonary artery (*Figure 4D*) with no evidence of pulmonary thromboembolism. Bilateral pleural effusion, pericardial effusion, and ascites were present. In addition, hepatosplenomegaly and lymphadenopathy in bilateral neck, axilla, mediastinum, and para-aorta were present (*Figure 4A–C*). Right heart catheterization (RHC) confirmed the presence of PAH (*Table 1*).

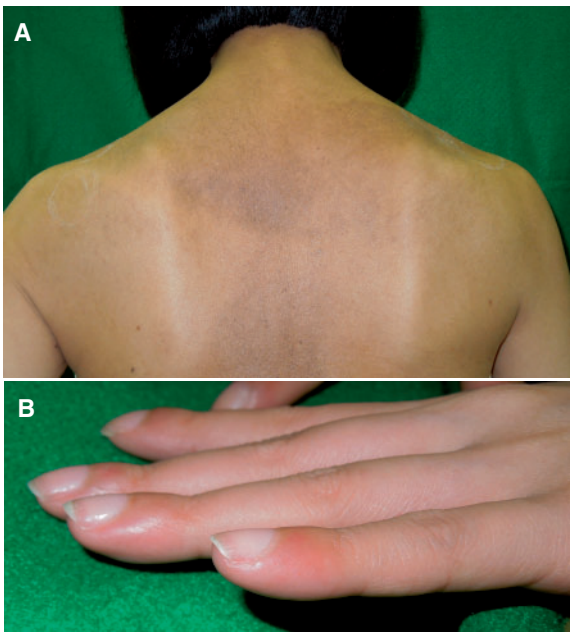


Figure 1 Skin pigmentation on the back (*A*) and the tip of fingers (*B*). Clubbed fingers on both hands (*B*).

To determine the aetiology of the patient's PAH, further evaluation was performed. Blood test revealed mild thrombocytosis with a platelet count of 388×10^3 cells/μL (normal reference value: 150–350×10^3 cells/μL). Serum HIV-1 titre and the antibody titre related to autoimmune disease were completely negative. Low free T3 and free T4 levels with high thyroid-stimulating hormone suggested hypothyroidism. Total serum immunoglobulin was normal with normal protein electrophoresis and a negative test of Bence Jones protein. There was elevation of κ and λ free light chain levels (55.0 mg/L and 33.2 mg/L, respectively) (normal reference value: 3.3–19.4 mg/L, 5.7–26.3 mg/L) with an increased light chain ratio (1.66) (normal reference value: 0.26–1.65). Notably, serum vascular endothelial cell growth factor (VEGF) level was significantly elevated. Computed tomography revealed multiple patchy osteosclerotic lesions in pelvic bone, vertebral body, costal bone, and sternal bone (*Figure 4E*).

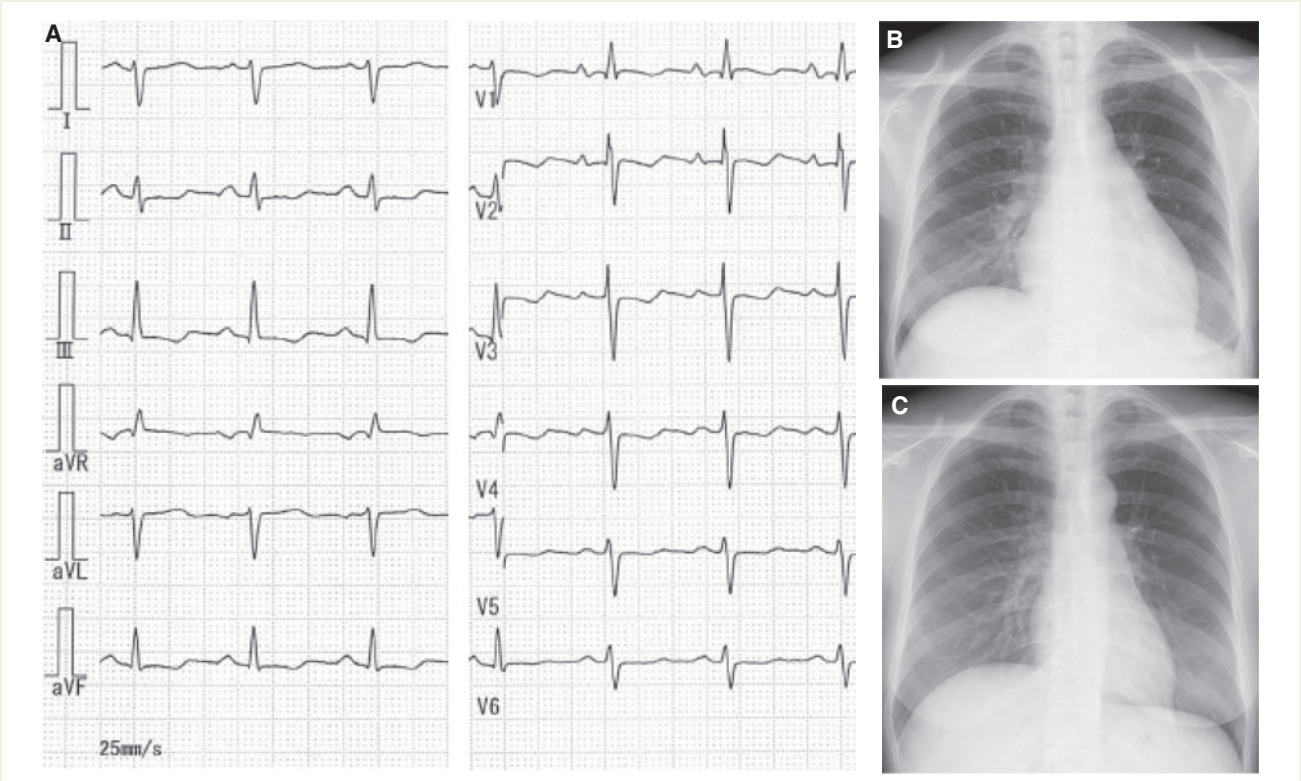


Figure 2 12-lead resting electrocardiogram on admission (*A*). Chest X-ray on admission (*B*) and 1 year following thalidomide and dexamethasone therapy (*C*).

Bilateral papilledema was present. In addition, although there was no clinical history suggestive of neuropathy, nerve conduction studies confirmed peripheral polyneuropathy involving the reduction in amplitude and velocity of sensory potentials and clear slowing of motor velocities with a decrease in amplitude in excess of 50%. All of these findings supported a diagnosis of POEMS syndrome according to the diagnostic criteria.[8]

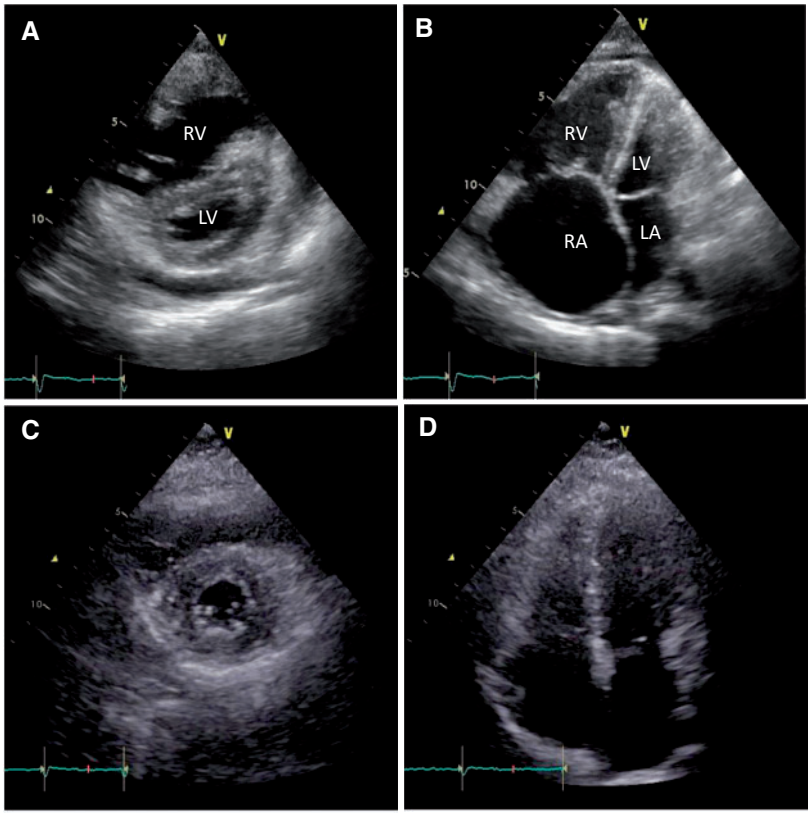
As symptoms and haemodynamics have not been improved with the initiation of tadalafil for PAH, our patient was started on immunomodulatory agent using thalidomide and dexamethasone. A year later, as a consequence, her symptoms of dyspnoea, pericardial effusion, pleural effusion, and ascites have completely disappeared with significant recovery of RV function (*Figures 2C* and *3C–E*) (Supplementary material online). PFT was recovered with a DLCO of 66.6% of predicted value. Furthermore, her current RHC indicated no evidence of PAH (*Table 1*).

Discussion

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare paraneoplastic disorder caused by plasma cell dyscrasia. Additionally, PAH is thought to be an uncommon feature of POEMS syndrome. Although there is weakness and/or numbness of the limb due to peripheral neuropathy, peripheral oedema and skin change were reported as the most common initial symptoms.[9] This is, to our knowledge, the first case reported in which PAH was the initial presentation in a patient with POEMS syndrome who was treated successfully with thalidomide and dexamethasone.

Contrary to the current diagnostic criteria of POEMS syndrome, monoclonal plasma cell dyscrasia was not detected in the present case. However, in spite of the absence of this type of dyscrasia, we consider this case to be consistent with POEMS syndrome for the following reasons. The first reason is the previous finding that 25% of cases of POEMS syndrome lack a monoclonal plasma cell disorder.[10] The second reason is the presence of typical clinical findings and a clinical course specific for a favourable response to immunomodulatory agents. Based on these factors, we assume that the present case might be a very early stage of POEMS syndrome with a characteristic finding of PAH.

The suggested prevalence of associated PH in POEMS syndrome is 27–48%,[5–7] although these figures were obtained using TTE to estimate pulmonary arterial systolic pressure (PASP), implying the prevalence of the PAH might be far less than these reports. A case similar to ours has been previously published, which mentions a PAH patient in the setting of POEMS syndrome, successfully treated with thalidomide and methylprednisolone.[11] However, contrary to our case,



E

	Before treatment	After treatment
RV diameter (mm)	35.6	24.0
RV area (cm^2)	22.4	13.2
TAPSE (mm)	10.2	20.3
FAC (%)	26.7	42.0
S' (cm/s)	7	14

Figure 3 Short-axis view and apical four-chamber view of transthoracic echocardiogram on admission (*A, B*) and 1 year following thalidomide and dexamethasone therapy (*C, D*). The size and function of right ventricle before and after treatment (*E*).

PAH in this report was diagnosed by TTE, not with RHC which is the standard diagnostic modality, suggesting lack of definitive evidence of PAH.

To date, despite the conflicting findings seen with anti-VEGF therapy, VEGF is the cytokine that correlates best with disease severity and treatment response of PH.[12] In our case, the serum level of VEGF was elevated at 4080 pg/mL (normal reference value; plasma VEGF 31–86 pg/mL,[13] serum VEGF < 1040 pg/mL[12]) and dropped significantly to 240 pg/mL over the year with treatment, accompanied by the significant improvement of other symptoms. Vascular endothelial cell growth factor was postulated to mediate PH with its vascular permeability causing interstitial and perivascular oedema and subsequent hypoxaemia inducing endothelial VEGF, completing a vicious cycle, eventually leading to PAH.[14] However, VEGF level might not be the driving force of the disease based on the conflicting findings seen with anti-VEGF therapy.[15–17]

With respect to available therapy, there are no standard treatments for POEMS syndrome. However, the patient was not considered as an ideal candidate for two recognized effective treatments.[18,19] Radiotherapy was rejected because of multiple bone lesions, and autologous stem-cell transplantation was rejected due to severe PAH.[7] More recently, thalidomide treatment has been shown to have decreased serum VEGF levels and improved clinical symptoms from randomized placebo-controlled trial.[20] Thalidomide has many effects that are potentially useful for the treatment of POEMS syndrome, including suppression of monoclonal plasma cell proliferation and modulation of upregulated cytokines[21]; however, how it contributes to the treatment for PAH remains uncertain.

Importantly, the effect on RV haemodynamics would be of profound significance in the recovery of RV failure. Before treatment, the patient was considered at high risk for PAH because of poor RV haemodynamics with relatively high right atrial pressure and low cardiac index (CI) in addition to poor RV function by TTE and CMR. After treatment with thalidomide and dexamethasone, reversal of PAH was obtained by RHC with a significant decrease of pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure. The substantial improvement of haemodynamics presumably led to the subsequent recovery of RV size and function confirmed by CMR.[22] This recovery is most likely due to inhibition of pressure/volume overload secondary to vascular permeability by immunomodulatory therapy, which is consistent with the significant reduction of serum VEGF levels.

Our report has a key limitation in its nature of single case study. Nevertheless, our case suggests that early diagnosis and intervention with thalidomide and dexamethasone have decreased PVR drastically in patients with severe PAH concomitant with POEMS syndrome and a subsequent improvement of symptoms. Accordingly, it would be important to consider associated syndromes when a diagnosis of

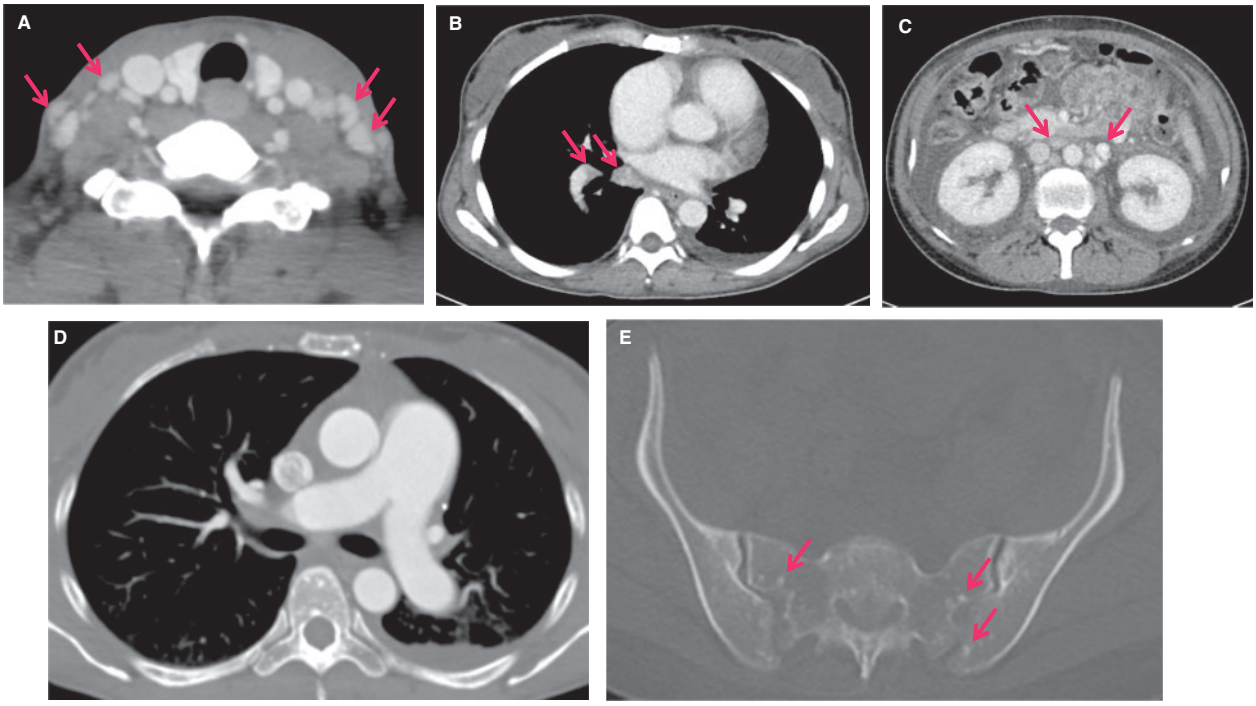


Figure 4 Multiple lymphadenopathy in the neck (*A*), mediastinum (*B*) and para-aorta (*C*, arrows). Significant dilatation of pulmonary artery (*D*). Multiple patchy osteosclerotic lesions in pelvic bone and vertebral body on computed tomography scan (*E*, arrows).

Table 1 Comparison of key haemodynamics and POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome-related parameters with thalidomide and dexamethasone therapy

Normal reference value	Before treatment	After treatment
WHO Classification	4	1
RHC		
RAP (mmHg)	14	2
PAP (mmHg)	89/40 (58)	24/5 (14)
PCWP (mmHg)	15	4
PA saturation (%)	65	76
PVR (WU)	12.6	2.9
CMR		
RVEF (50–65%)	47	61
RVEDV (85–168 mL)	166	93
serum VEGF (<1040 pg/mL)	4080	240
BNP (<18.4 pg/mL)	430.9	23.2
DLCO (80–120%)	30.4	66.6

RHC, right heart catheterization; RAP, right atrial pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PA saturation, pulmonary arterial saturation; PVR, pulmonary vascular resistance; CMR, cardiac magnetic resonance; RVEF, right ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; VEGF, vascular endothelial cell growth factor; BNP, brain natriuretic peptide; DLCO, diffusing capacity of the lungs for carbon monoxide.

PH is made, because treatment of the underlying condition may lead to improvement in PAH.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Acknowledgements

The authors are grateful to Dr Tomohisa Nagoshi and Dr Tohru Sakuma at Jikei University School of Medicine for their editing contribution. We also are grateful to Prof Marius Hoeper at Hannover Medical School and Dr Yuichi Tamura at International University of Health and Welfare Mita Hospital for their suggestion of diagnostic workup.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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