

[CASE REPORT]

POEMS Syndrome Showing Left Ventricular Dysfunction and Extracellular Edema Assessed by Cardiac Magnetic Resonance Imaging

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Abstract:

Although cardiac involvement is rare in polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome, the clinical course becomes considerably worse on complication with cardiac lesions. The increased release of various cytokines has been observed in the pathogenesis of POEMS syndrome, and serum vascular endothelial growth factor (VEGF) levels are known to be associated with the disease activity. We herein report a patient with POEMS syndrome who showed left ventricular systolic dysfunction and was treated with lenalidomide therapy. Of note, the reduction in extracellular edema in the left ventricular wall was clearly visualized by changes in the native T1 values and extracellular volumes on cardiac magnetic resonance imaging.

Key words: POEMS syndrome, vascular endothelial growth factor, native T1 mapping, extracellular volume

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Introduction

polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome, a rare multisystem disorder, is very occasionally complicated with cardiac lesions. However, the mortality rate increases sharply once heart failure develops. Therefore, the early identification and subsequent treatment of cardiac lesions is important in the management of POEMS syndrome. The increased release of cytokines, such as vascular endothelial growth factor (VEGF), interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF)- α , is implicated in the pathogenesis of POEMS syndrome (1).

Of note, serum VEGF levels are known to be increased in POEMS syndrome and correlate with the disease activity. Given the main function of VEGF-enhancement of the vascular permeability-its overexpression could cause interstitial edema in various organs. However, little is known about

whether or not cardiac interstitial edema can be detected using cardiac magnetic resonance imaging (MRI), which was recently developed to identify the pathologic features of various cardiac diseases.

We herein report a patient suffering from POEMS syndrome complicated with a cardiac lesion manifesting left ventricular (LV) edema and systolic dysfunction that was able to be well evaluated using cardiac MRI. This case highlights the clinical relevance of assessing the extracellular fluid volume by T1 mapping as well as the extracellular volume in the management of cardiac lesions associated with POEMS syndrome.

Case Report

A 53-year-old Japanese woman a medical history of hypertension was admitted to our hospital due to exertional dyspnea and systemic edema. She had been diagnosed with POEMS syndrome 6 months earlier based on polyneuropathy

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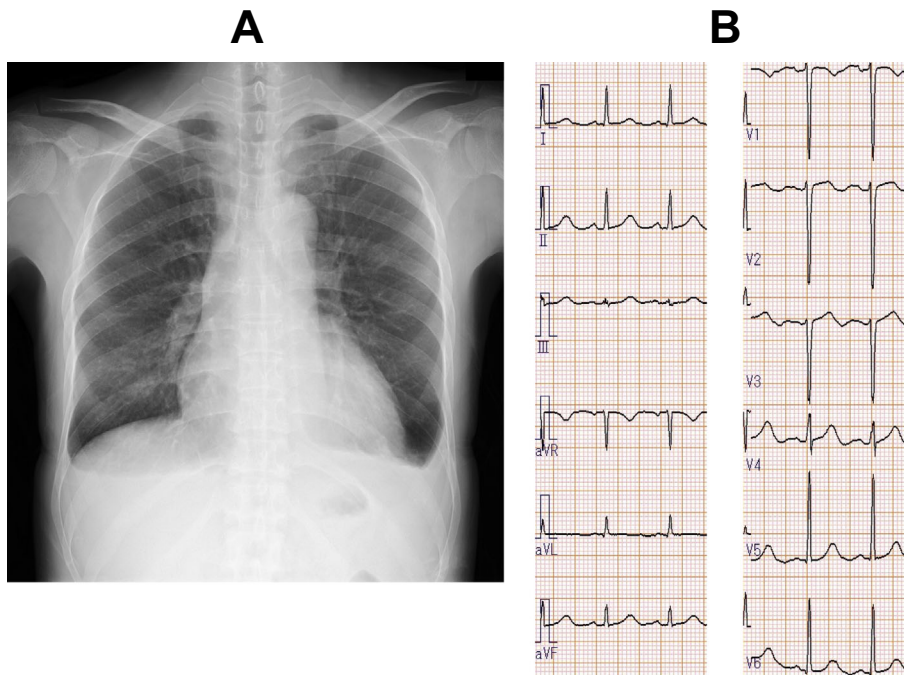


Figure 1. Chest X-ray (A) and electrocardiogram (B) findings of the patient before the treatment.

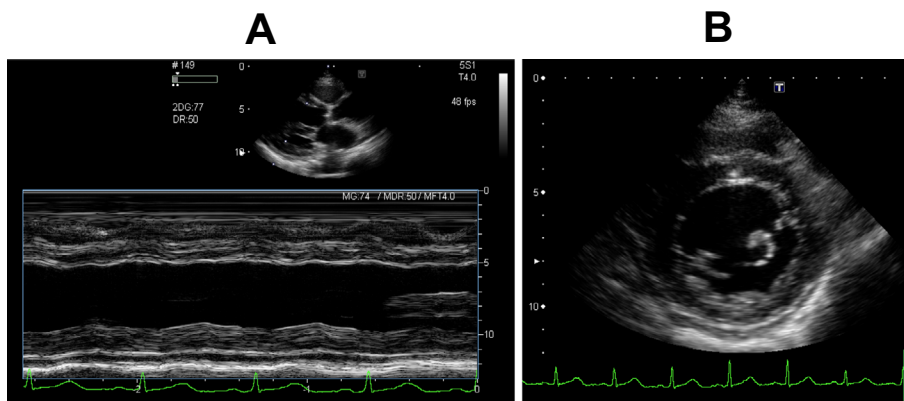


Figure 2. Echocardiographic images before the treatment. A: M-mode recording of the basal left ventricle showing a mildly enlarged left ventricle as well as diffuse hypokinesia of the wall motion. B: Two-dimensional parasternal short-axis view of the basal left ventricle showing normal thickness of the left ventricular wall along with mild pericardial effusion.

thy, prominent M protein, and elevated serum VEGF levels of 5,390 pg/mL (normal range: <38.3 pg/mL). At that time, she had a normal cardiac function with an LV ejection fraction of 60% and a slight increase in the plasma B-type natriuretic peptide (BNP) level (99 pg/mL).

On admission, her blood pressure was 161/102 mmHg, and her heart rate was 92 beats/min with a regular rhythm. A physical examination revealed marked bilateral leg edema, skin hyperpigmentation, and hepatosplenomegaly. On auscultation, an S3 gallop rhythm with moist lung crackles was noted. A neurological examination showed mild motor weakness and hypoesthesia of the extremities with a reduced deep tendon reflex. Chest X-ray revealed mild cardiomegaly and bilateral pleural effusion (Fig. 1A). An electrocardiogram showed high voltage in precordial leads (Fig. 1B).

Echocardiography showed diffuse hypokinesia of the LV with a 35% ejection fraction and increased indexed LV mass (123 g/m²) despite a normal LV wall thickness, suggesting eccentric hypertrophy (Fig. 2). Plasma BNP and serum VEGF levels were elevated to 322.8 pg/mL and 4,300 pg/mL, respectively. 3-Tesla (3T) cardiac magnetic resonance (CMR) imaging with T1 mapping demonstrated globally increased myocardial native T1 values (1,350-1,450 msec) compared with controls (1,150-1,300 msec) without a pronounced region of gadolinium enhancement. The cardiac extracellular volume (ECV) was 0.34, which was significantly higher than the institute's normal range (Fig. 3).

Coronary artery disease was ruled out by coronary angiography. Right heart catheterization showed that the pulmonary artery wedge pressure, pulmonary arterial pressure, and

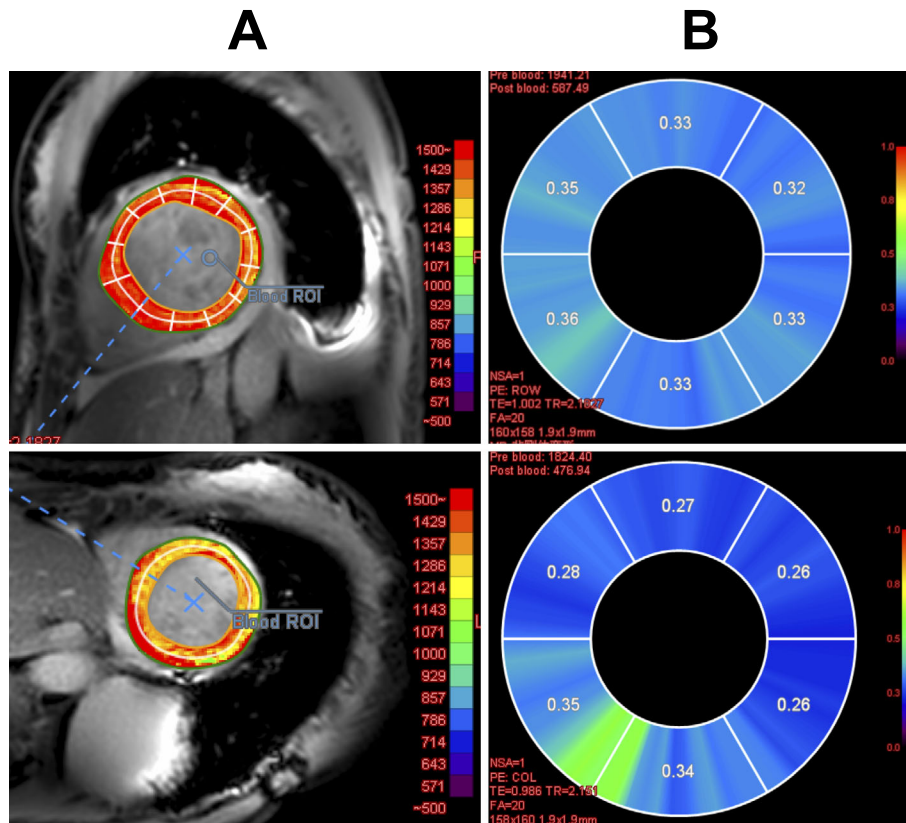


Figure 3. Cardiac magnetic resonance imaging before and after the treatment. A: Polar mapping of the native T1 values of the left ventricle before the treatment (top) showing diffuse enhanced T1 value of around 1,400 msec and that after the treatment (bottom) showing a shortened T1 value of around 1,300 msec. B: Polar mapping of the extracellular volume (ECV) before (top) and after (bottom) the treatment showing a reduction in the ECV of the whole segment of the left ventricle by the treatment. Because of the increase in the indicated value around the inferior segment after the treatment due to an image artifact, the ECVs at the inferior and inferolateral segments were higher than the actual values.

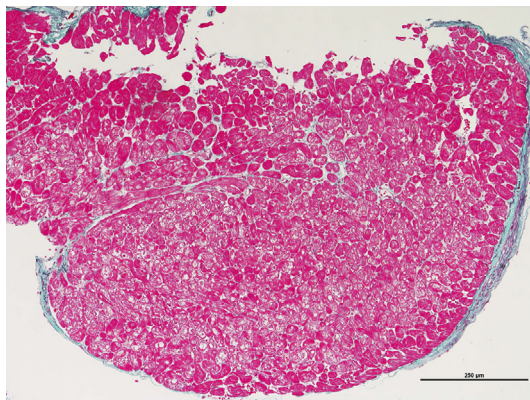


Figure 4. Histopathology of a right ventricular endomyocardial biopsy. Elastica-Masson stain of an endomyocardial biopsy showed slight fibrosis around the vessels.

right arterial pressure were within their respective normal ranges, and the cardiac index was preserved at 2.89 L/min/m². The histopathology of a right ventricular endomyocardial biopsy showed mild myocardial hypertrophy and fibrosis without inflammatory cells, granuloma, or abnormal proteins

(Fig. 4). Subsequent direct fast scarlet staining confirmed no evidence of amyloid deposition. Based on these findings, ischemic heart disease, amyloidosis, sarcoidosis, and myocarditis were excluded. Although she had a history of hypertension, hypertensive changes in the fundus and other atherosclerotic lesions were not evident, suggesting a low possibility of hypertensive heart disease. Therefore, the etiology of the heart disease was diagnosed as POEMS syndrome-related myocardial injury.

Since our case was considered to have a high risk of cardiac events during high-dose chemotherapy due to her low cardiac function, we started her on the thalidomide derivative lenalidomide (15 mg/day) with intravenous dexamethasone (40 mg/week) instead of the usual high-dose chemotherapy for POEMS syndrome. In addition, enalapril (2.5 mg/day) and carvedilol (1.25 mg/day) were started for LV systolic dysfunction and titrated up to 5.0 and 10 mg/day, respectively.

On the 10th day after the initiation of the treatment, follow-up T1 mapping showed reduced native T1 values (1,300-1,350 msec) in accordance with dramatic decrease in plasma BNP to 20 pg/mL and serum VEGF level to 1,070

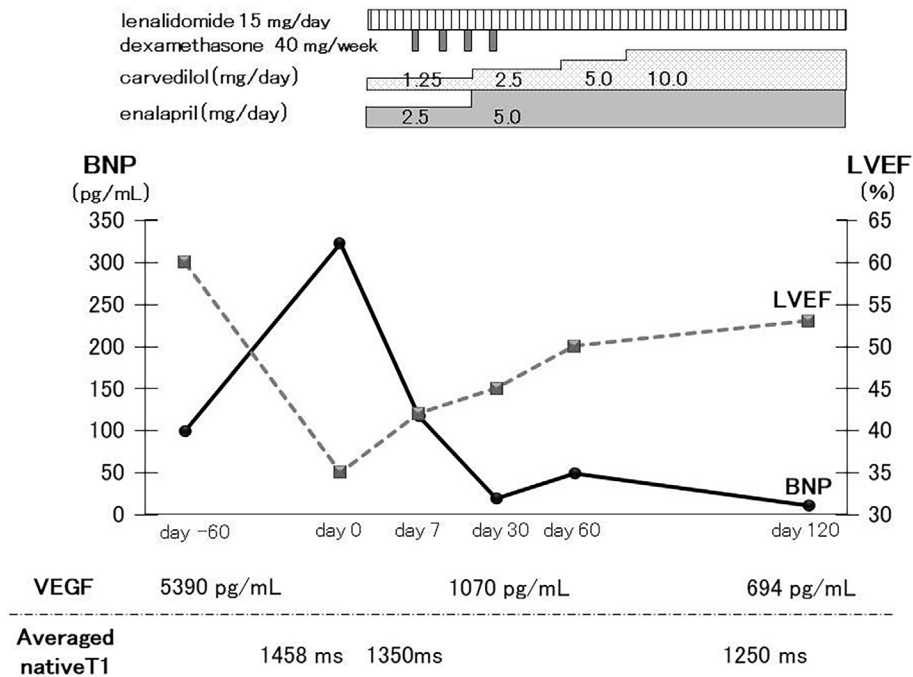


Figure 5. Patient's clinical course. Despite the obvious reduction in the left ventricular ejection fraction (dotted polygonal line) and increase in the plasma BNP level (solid polygonal line) along with the enhanced serum VEGF level before the treatment, the left ventricular ejection fraction gradually increased while the plasma BNP level rapidly decreased following the administration of lenalidomide, dexamethasone, carvedilol, and enalapril. The serum VEGF level was also reduced in response to the treatment. The prolonged native T1 value on cardiac magnetic resonance imaging was shortened at day 10 from 1,458 to 1,350 msec on average. BNP: brain natriuretic peptide, LVEF: left ventricular ejection fraction, VEGF: vascular endothelial growth factor

pg/mL. Twenty days after the treatment, her body weight had decreased by 9 kg, and systemic edema was completely diminished. After 2 months, echocardiography showed significant improvement in the LV ejection fraction to 50%, and she was discharged without any residual symptom (Fig. 5). Two months later, cardiac MRI showed a reduction in the native T1 value along with the decrease in the ECV (0.29), suggesting relief of the extracellular edema in the left ventricle (Fig. 3). She currently maintains a stable condition of POEMS syndrome without any recurrence of heart failure.

Discussion

POEMS syndrome is a rare multisystem disorder that is considered to be related to multiple myeloma complicated with organomegaly, endocrinopathy, M protein, and skin changes. Multiple cytokines, such as IL-1 β , IL-6, TNF- α , have been considered to be responsible for the characteristic symptoms, and VEGF has been reported to play a main role in the disease activity (1).

Regarding the cardiovascular systems, although pulmonary hypertension is often found in POEMS syndrome (2, 3), cardiac involvement is quite rare. To our knowledge, only eight cases of POEMS syndrome complicated with heart failure have been reported thus far (4-11).

Among these, the cardiac manifestations have varied, including dilated LV with systolic dysfunction (4, 6, 9) and LV hypertrophy with or without systolic dysfunction (5, 8, 10, 11). There are two possible reasons for this variation: that different stages of the same serial changes in the LV morphology have been observed, or that different cytokines contributed to the disease progression.

Of note, only one of these previous cases showed a similar clinical course to our own patient, namely transient LV systolic dysfunction, which was managed by the administration of thalidomide treatment (11). That case and our own may share the same mechanism underlying the progression and regression of the LV systolic dysfunction: extracellular edema due to the overexpression of VEGF in the myocardial wall. Because VEGF is known to enhance the vascular permeability in various organs, excessive VEGF production may cause extracellular edema, resulting in systolic dysfunction due to myocardial ischemia induced by the extension of the distance from the capillary to the myocardium. The present MRI findings, in which the elevated native T1 value and ECV were both attenuated in the pathological lesion by treatment, along with the presence of only slight fibrosis seem to support this hypothesis.

Of note, this is the first report in which the changes in extracellular edema in POEMS syndrome were clearly visualized using 3T MRI with consultation of the recently devel-

oped native T1 and ECV values.

Informed consent was obtained from this patient for publication of this case report and associated images.

The authors state that they have no Conflict of Interest (COI).

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