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Case Report

Frontline Autologous Stem Cell Transplantation in POEMS Syndrome with Pulmonary Arterial Hypertension

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Abstract

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin change (POEMS) syndrome is a rare para-neoplastic syndrome related to plasma cell disorder. Pulmonary arterial hypertension (PAH) is a cardiovascular comorbidity caused by underlying plasma cell disorder. Targeted therapy aimed at plasma cells may be more beneficial than treating POEMS syndrome with conventional PAH therapy. We present the case of a 47-year-old woman who was diagnosed with POEMS syndrome complicated with PAH and treated with myeloma-like therapy followed by autologous stem cell transplantation (ASCT). This case highlights that targeted therapy against plasma cells and frontline ASCT may be beneficial with regards to the clinical outcomes.

Keywords: Autologous stem cell transplantation, polyneuropathy organomegaly endocrinopathy monoclonal gammopathy and skin change syndrome, pulmonary arterial hypertension

Introduction

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin change (POEMS) syndrome is a rare para-neoplastic syndrome often associated with plasma cell disorder. Polyneuropathy and monoclonal gammopathy are often considered as mandatory diagnostic criteria, and other features including extravascular fluid overload, papilledema, or sclerotic bone change are important disease presentations. Pulmonary arterial hypertension (PAH) is a cardiovascular comorbidity related to POEMS syndrome, with a reported prevalence of around 27%–36%.[1,2] Patients diagnosed with PAH often need life-long treatment including calcium channel blockers, endothelin receptor antagonists, prostacyclins, and phosphodiesterase Type 5 inhibitors.[3] Targeted therapy for plasma cell disorders may reverse the clinical course. Herein, we present a case of POEMS syndrome with PAH who recovered after induction therapy with bortezomib, thalidomide, and dexamethasone (VTD) followed by autologous stem cell transplantation (ASCT).

Case Report

A 47-year-old woman presented with a past history of hypothyroidism which had been treated at a local

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clinic with levothyroxine. She did not smoke or drink alcohol. She reported dizziness, fatigue, numbness, and progressive shortness of breath for months. Transthoracic echocardiography suggested PAH, with a mean pulmonary arterial pressure (PAP) of 39 mmHg [Figure 1a]. Multi-detector computed tomography and cardiac catheterization was performed, which revealed no coronary lesions, valvular heart disease, pulmonary fibrosis, or pulmonary thromboembolism, but multiple spinal osteosclerotic lesions [Figure 2] with a fluffy appearance were found. Serum immunofixation (IFE) revealed subtle immunoglobulin A (IgA)-lambda monoclonal gammopathy [Figure 3a]. A bone marrow examination revealed normo- to hypercellularity with adequate tri-lineage maturation but a few lambda light chain restricted plasma cells without clustering or exceeding 10% under CD138 immunohistochemistry staining were noted [Figure 4a-d]. No myeloma-defining events were recorded, such as anemia, hypercalcemia, or deteriorating renal function. Nerve conduction velocity and electromyography showed polyneuropathy with demyelinating change. According to these clinical findings, she was diagnosed with POEMS syndrome with the presentation of PAH.

The patient received weekly VTD triplet therapy for four consecutive months, and the initial symptoms improved. A bone marrow examination after induction therapy showed the disappearance of lambda-restricted plasma cells, and serum IFE revealed an absence of monoclonal gammopathy [Figure 3b]. She then received high-dose cyclophosphamide (1500 mg/m^2 for two consecutive days) and granulocyte colony-stimulating factor for stem cell harvest. Sufficient peripheral blood progenitor cells were collected with 6.76^10^6 CD34 cells/kg in single leukapheresis. She underwent ASCT conditioned with a melphalan-200 regimen, and leukocytes were engrafted on day 11 without serious adverse events. Echocardiography revealed a mean PAP of 30 mmHg about 4 months post transplantation [Figure 1b]. Two years after ASCT, echocardiography revealed a mean PAP of 24 mmHg [Figure 1c]. No transplant-related complications were noted during 2-years of follow-up, and serial serum IFE evaluations still showed an absence of monoclonal gammopathy [Figure 3c].

Discussion

POEMS syndrome is a relatively rare disease, and there is currently no consensus on treatment. In addition, no prognostic stratification scales have been established, but widely recognized risk factors including age above 50 years, estimated glomerular filtration rate <30 ml/min/1.73 m^2, pleural effusion, and pulmonary hypertension may be related to worse outcomes.[4] Although the treatment response may be correlated with vascular endothelial growth factor (VEGF) level, targeting the underlying plasma cell disorder may lead to better outcomes than treatment with anti-VEGF antibodies.[2] Due to the scarcity of qualified randomized prospective clinical trials, treatment for POEMS syndrome varies. POEMS syndrome without disseminated bone marrow involvement may be cured by radiation. In a case series of patients diagnosed with POEMS syndrome with limited bone marrow involvement, radiation as the primary treatment resulted in a four-year overall survival rate of 97% and 4-year event-free survival rate of 52%.[5]

The treatment of multiple myeloma has continued to improve, and the general treatment for POEMS syndrome is similar to that for myeloma due to the background plasma cell disease etiology. The treatment options include alkylating agents, proteasome inhibitors, immunomodulating drugs, and corticosteroids. Eligible patients may receive ASCT with melphalan conditioning with dosages ranging from 140 to 200 mg/m^2, determined according to the patient's status. In a retrospective study comparing three first-line regimens

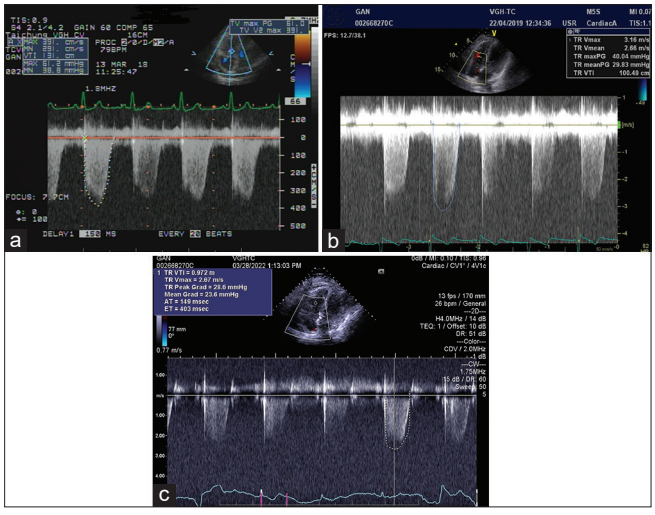

Figure 1: Comparison between transthoracic echocardiography at (a) Initial presentation (b) 4 months after ASCT and (c) 2 years after ASCT. ASCT: Autologous stem cell transplantation

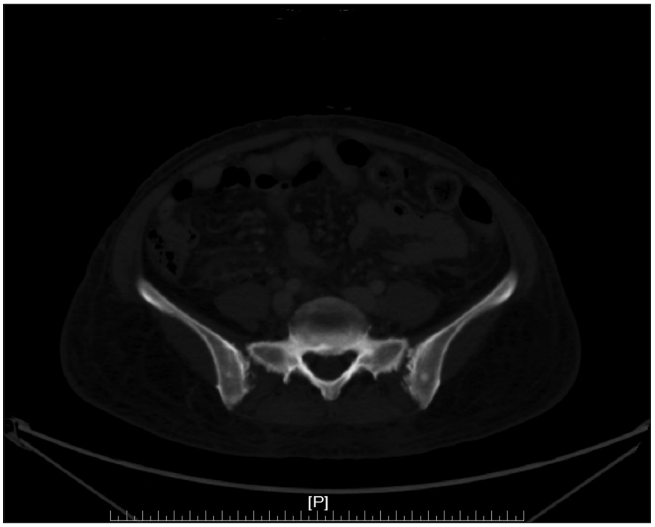

Figure 2: Osteosclerotic lesion with a fluffy appearance noted on MDCT. MDCT: Multi-detector computed tomography

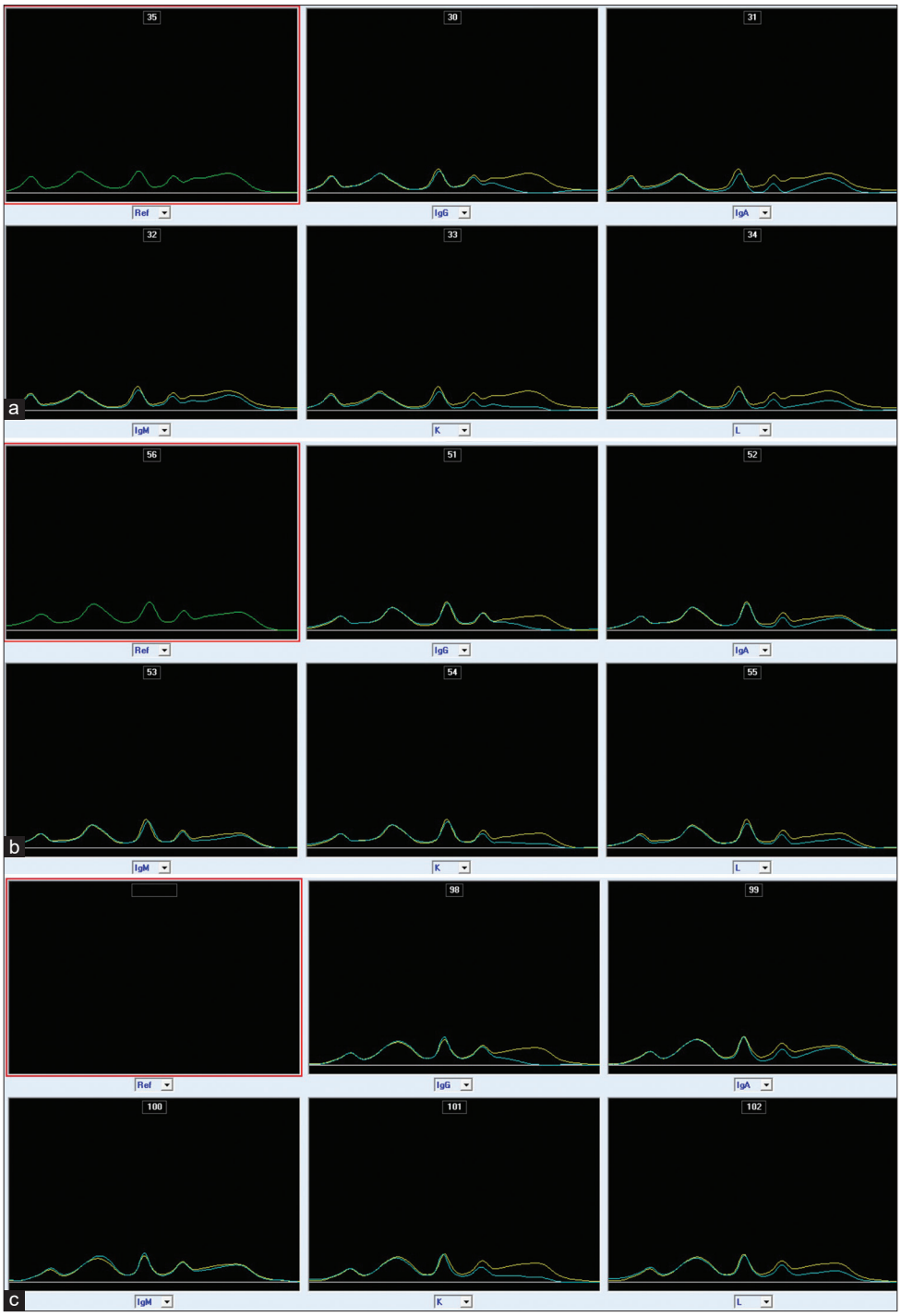

Figure 3: Comparison between serum IFE at (a) Initial presentation (b) Completion of VTD induction therapy and (c) 2 years after ASCT. IFE: Immunofixation, VTD: Bortezomib, thalidomide and dexamethasone, ASCT: Autologous stem cell transplantation

including ASCT, melphalan with dexamethasone, and lenalidomide with dexamethasone, there were no significant differences in 3-year overall survival difference, but frontline ASCT contributed to better three-year progression-free survival and complete hematological remission in medium to high-risk patients.[6]

In a retrospective study, the prevalence of PAH in patients with POEMS syndrome as confirmed by transthoracic echocardiography was 27%.[1] In 23 patients with both documented PAP and VEGF level, PAP decreased from 57 to 30 mmHg and VEGF level decreased from 3573 to 379 pg/ml after treatment. There was a correlation between PAP and VEGF level, and VEGF may be related to microvascular hyper-permeability and endothelial dysfunction. However, although there is still no confirmed pathophysiology between VEGF and PAH, both features are considered

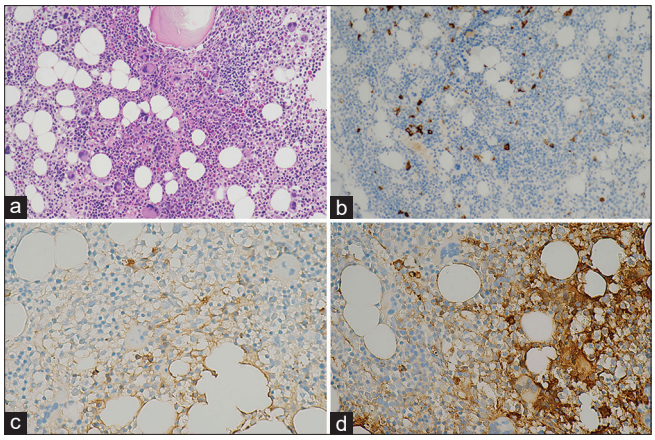

Figure 4: Bone marrow pathology revealed (a) Normo- to hypercellularity with normal tri-lineage maturation under × 200 (b) No plasma cell clustering or exceeding 10% composition under CD138 immunohistochemistry staining (c) Kappa and (d) Lambda staining revealed lambda light chain restricted plasma cells without clonal proliferation

to be consequences related to cytokine secretion by an underlying plasma cell disorder. Therefore, targeted therapy for the underlying plasma cell disorder may better control the disease than conventional PAH treatment. Similar to POEMS syndrome without disseminated bone marrow involvement managed by radiation, a case report of POEMS syndrome with the initial presentation of PAH but refractory to conventional PAH therapy showed that radiation treatment to a bone lesion could also be used.[7]

We treated our patient with the VTD regimen, and PAP improved from 39 to 30 mmHg after induction therapy. She tolerated the VTD courses and was eligible for ASCT due to her improving condition. ASCT was done using a melphalan-200 protocol, and PAP further improved to 24 mmHg after 2 years of follow-up. POEMS syndrome patients may sometimes be ineligible for ASCT due to severe PAH or other comorbidities.[8] The use of a predictive comorbidity index of hematopoietic cell transplantation may guide physicians to perform ASCT, but more evidence is required to evaluate frailty among POEMS syndrome patients with PAH in a real-world setting.[9] Serum IFE revealed that IgA-lambda light chain gammopathy resolved after induction therapy and remained undetectable during follow-up. Our case suggests the feasibility of induction therapy followed by ASCT for patients with POEMS syndrome with PAH.

Conclusion

Targeted therapy such as myeloma treatment with VTD induction followed by ASCT is beneficial for patients diagnosed with POEMS syndrome with pulmonary hypertension.

Declaration of patient consent

The authors certify that we have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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