CASE REPORT

Reduction of Optic Disc Oedema by Bortezomib and Dexamethasone Followed by Autologous Peripheral Blood Stem Cell Transplantation in Patient with POEMS Syndrome

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ABSTRACT

The authors present findings in a 39-year-old man with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome with bilateral optic disc oedema. He was successfully treated with bortezomib and dexamethasone followed by autologous peripheral blood stem cell transplantation. The peripapillary retinal thickness was reduced in the optical coherence tomographic (OCT) images along with a decrease of the serum vascular endothelial growth factor (VEGF) levels. The authors recommend OCT to monitor the changes in the signs of POEMS syndrome after treatments.

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Introduction

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare paraneoplastic disorder caused by a plasma cell disorder.¹ The pathogenesis of the POEMS syndrome has not been conclusively determined, but an overproduction of vascular endothelial growth factor (VEGF) has been suggested.² The major ocular finding in POEMS syndrome is optic disc oedema (ODE).³

It has been reported that spectral-domain optical coherence tomography (SD-OCT) can be used to detect and quantify the degree of ODE by determining the peripapillary retinal nerve fibre layer (pRNFL) or the peripapillary retinal thickness (pRT).^{4–6} Several studies have documented the improvement of the ODE in patients with POEMS syndrome by fundus photographs after treatments with radiation, thalidomide, and autologous peripheral blood stem cell transplantation. However, the degree of the ODE has not been determined by OCT,^{7, 8} although there was a report that the ODE and macular oedema were

followed by OCT in patients with the POEMS syndrome. Unfortunately, they did not observe an improvement of the ODE.⁹

The purpose of this report is to present our findings in a patient with the POEMS syndrome who was successfully treated with bortezomib and dexamethasone followed by autologous peripheral blood stem cell transplantation. We followed the reduction of the ODE objectively and quantitatively by measuring the changes of the pRT by SD-OCT before and after the treatments.

Case report

A 39-year-old treatment-naïve man with the POEMS syndrome was admitted to our hospital because of being diagnosed with the POEMS syndrome that was made by the internal medicine department based on the presence of polyneuropathy, high serum level of VEGF, skin changes, pleural effusion, and plasmacytoma. He presented in our department with blurred vision and decimal best-corrected visual acuities (BCVAs) of 0.9 OD and 1.0 OS. The ophthalmic

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examinations showed bilateral ODE (Figure 1A), hyperpermeability of the optic disc in the early and late phases of fluorescein angiography (Figure 1B, C), and macular oedema (Figure 1D). The pRT was measured with the RS3000 advanced spectral-domain OCT (SD-OCT; NIDEK, Gamagori City, Japan) to quantify the degree of the ODE. A 3.45-mm-diameter circular scan centred on the optic disc ("Disc Circle" mode, software NAVIS-EX V.1.5.0) was recorded through a dilated pupil. The scan consisted of 1024 A-scans with high-definition (50 HD) frame enhancement software that measured the pRT along a circle around the optic disc. The pRT was measured automatically as the distance between the internal limiting membrane and the outer border of the retinal pigment epithelium with the software in the RS3000 SD-OCT. The pRT of this patient was 1062 μm in the right eye and 963 μm in the left eye (Figure 1E). The average pRT in normal control eyes has been reported to range from 274.23 to 283.51 μm (right eye) and 274.99 to 289.96 μm (left eye) in a previous study.⁵

He was given 1.3 mg/m^2 bortezomib intravenously on days 1, 4, and 8. He was also given 11 plus 40 mg of dexamethasone orally on days 1 through 4 and 9 through 12 (cycle 1), 21-day cycle. Because of the adverse effects of this regimen, e.g., hepatopathy, subileus, and leg pain, the dose was reduced to 8 mg/day dexamethasone and 1.0 mg/m^2 bortezomib from cycle 3. After four cycles of bortezomib and dexamethasone therapy, he was given high-dose melphalan therapy followed by autologous peripheral blood stem cell transplantation. After 3 months of this treatment protocol, the serum VEGF level was reduced from 9960 to 269 pg/mL, and the ODE and macular oedema were improved. In addition, the pRT was reduced to 406 μm in his right eye and 358 μm in his left eye (Figure 2A, B). After 6 months of the treatment, the serum VEGF level was 333 pg/mL, the ODE and macula oedema were improved (Figure 3A, B), and the pRT was reduced to 406 μm in his right eye and 358 μm in his left eye (Figure 3C). His BCVA improved to 1.2 in both eyes. The

Figure 1. Ocular findings in a patient with the polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome. (A) Fundus photographs showing bilateral optic disc oedema. (B) Early phase of fluorescein angiogram showing leakage on the optic disc. (C) Late phase of fluorescein angiogram showing leakage on the optic disc. (D) Horizontal optical coherence tomographic (OCT; Heidelberg SPECTRALIS) images showing bilateral optic disc oedema and macular oedema. The green line is the horizontal line. (E) Optical coherence tomographic (OCT; NIDEK RS-3000) image showing the optic nerve head is approximately 3.45 mm in diameter circle (red circle) and the peripapillary retinal thickness (pRT). Red line and purple line represent the OCT outlining the pRT: the red line represents the inner border of internal limiting membrane line and the purple line represents the outer border of retinal pigment epithelium line.

Figure 2. Ocular findings in the patient with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome 3 months after the treatment. (A) Fundus photographs show that the bilateral optic disc oedema is resolved compared with that in [Figure 1A](#). (B) Optical coherence tomographic (OCT; NIDEK RS-3000) image showing the optic nerve head is approximately 3.45 mm in diameter circle (red circle) and the peripapillary retinal thickness (pRT). Red line and purple line represent the OCT outlining the pRT: the red line represents the inner border of internal limiting membrane line and the purple line represents the outer border of retinal pigment epithelium line. OCT image demonstrates a decrease in the peripapillary retinal thickness (pRT) compared with that in [Figure 1E](#).

polyneuropathy, skin changes, pleural effusion, and plasmacytoma also improved. During the 12-month follow-up, there were no recurrences of the ODE and the systemic symptoms and signs.

Discussion

The treatment of the POEMS syndrome is similar to that for multiple myeloma and light chain amyloidosis.¹⁰ Thalidomide therapy has been shown to be safe and efficacious in patients with POEMS syndrome,¹¹ as has radiation, melphalan, corticosteroids, cyclophosphamide, lenalidomide, bortezomib, and bevacizumab, an anti-VEGF agent.¹⁰ Bortezomib is a proteasome inhibitor with significant activity against multiple myeloma. The proteasomes are responsible for degrading the proteins that regulate essential cellular functions, such as cell cycling, proliferation, survival, and apoptosis. The inhibition of the proteasomes may activate programmed cell death in neoplastic cells by preventing the degradation of the pro-apoptotic factors.¹² They also inhibit the increased expression of pro-inflammatory and pro-angiogenic cytokines.^{12,13}

Bortezomib with dexamethasone and high-dose chemotherapy with autologous peripheral blood stem cell transplantation have also been reported to be efficacious in treating patients with the POEMS syndrome.^{13,14} In addition, autologous peripheral blood stem cell transplantation has been used to restore haematopoiesis following high-dose chemotherapy and radiotherapy.¹⁵ Similar results were obtained with our patient.

There have been several studies that reported that SD-OCT can identify and quantify the degree of ODE by measuring the retinal nerve fibre layer (RNFL) thickness.^{4,5} But in patients with a very thick RNFL, the outer border of the RNFL can be attenuated and undetectable. In such cases, measuring the peripapillary total retinal thickness might be a better way to quantify the degree of ODE.^{5,6}

It has been reported that there was a significant correlation between the serum VEGF levels and the ODE in patients with POEMS syndrome.⁶ Although these findings cannot answer the question of a cause-and-effect relationship between ODE and elevated VEGF, it was also reported that the resolution of the ODE in a patient with the POEMS syndrome was

Figure 3. Ocular findings in the patient with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome 6 months after the treatment. (A) Fundus photographs show that the bilateral optic disc oedema is resolved compared with that in [Figure 1A](#) and [Figure 2A](#). (B) Optical coherence tomographic (OCT) images show that bilateral macular oedema is resolved. (C) Optical coherence tomographic (OCT; NIDEK RS-3000) images showing the optic nerve head is approximately 3.45 mm in diameter circle (red circle) and the peripapillary retinal thickness (pRT). Red line and purple line represent the OCT outlining the pRT: the red line represents the inner border of internal limiting membrane line and the purple line represents the outer border of retinal pigment epithelium line. OCT images demonstrate a decrease in the peripapillary retinal thickness (pRT) compared with that in [Figure 1E](#) and [Figure 2B](#).

accompanied by a reduction in the serum VEGF level after thalidomide treatment.⁸ In our case, bortezomib and autologous peripheral blood stem cell transplantation also led to a decrease in the serum VEGF levels accompanied by a decrease in the pRT. Because the optic disc oedema was still present at 3 months after beginning the treatments, the pRT continued to decrease after the serum level of VEGF decreased to within the normal level. These results support the hypothesis that the ODE in patients with the POEMS syndrome is caused by the high levels of serum VEGF.

Although patients with the POEMS syndrome have been shown to have an overload of systemic extravascular fluid, e.g., peripheral oedema, pleural effusions, ascites, and pericardial effusions, the ODE and increased choroidal thickness^{8,16,17} were the only structural abnormalities in the eyes.

In our case, we did not find an increase in the vascular permeability of the peripheral retinal vessels. The reason for this might be because of a differential distribution of the VEGF receptors and the anatomy of the tissues surrounding the optic nerve head (ONH). The VEGFR1 and VEGFR2, both VEGF receptors, have different apicobasal distribution at blood-neural barriers. The majority of VEGFR1 is found on the apical (luminal) side, and the majority of VEGFR2 is found on the basal (abluminal) side of the barriers. Only VEGFR2 can increase the permeability, whereas VEGFR1 facilitates cytoprotection.¹⁸ We have reported that the serum level of VEGF was correlated with the subfoveal choroidal thickness.^{16,17} In the choroidal vessels, serum with a high concentration of VEGF could leak into the choroidal interstitial fluid through the fenestrated choriocapillaris, and the VEGF could

increase the permeability by affecting VEGFR2. It was reported from the findings in animal experiments that the blood stream reaches the axons of the optic nerve through the border tissue of Elschnig from the adjacent choroidal tissues.¹⁹ VEGF can leak into the ONH through the border tissues of Elschnig where it can increase the permeability of the capillaries of the ONH by affecting the VEGFR2 on the abluminal side, whereas the permeability of the retinal capillaries is not affected by VEGFR1 on the luminal side.²⁰ Our fluorescein angiography findings also showed that the leakage was limited to the region around the ONH.

We observed a reduction of the ODE by measuring the pRT in the SD-OCT images. It has been reported that serum VEGF level at 6 months after autologous peripheral blood stem cell transplantation or thalidomide treatment might be a predictive biomarker for disease activity and prognosis in POEMS syndrome.²¹ Therefore, if there is a correlation between the serum VEGF and pRT, SD-OCT would be a helpful method to objectively and noninvasively follow patients with POEMS syndrome after treatment.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

References

- [1] Dispenzieri A. POEMS syndrome. *Blood Rev* 2007;21:285–299.
- [2] Watanabe O, Arimura K, Kitajima I, Osame M, Maruyama I. Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome. *Lancet* 1996;347:702.
- [3] Kaushik M, Pulido JS, Abreu R, Amselem L, Dispenzieri A. Ocular findings in patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome. *Ophthalmology* 2011;118:778–782.
- [4] Menke MN, Feke GT, Trempe CL. OCT measurements in patients with optic disc edema. *Invest Ophthalmol Vis Sci* 2005;46:3807–3811.
- [5] Skau M, Milea D, Sander B, Wegener M, Jensen R. OCT for optic disc evaluation in idiopathic intracranial hypertension. *Graefes Arch Clin Exp Ophthalmol* 2011;249:723–730.
- [6] Yokouchi H, Baba T, Misawa S, Sawai S, Kitahashi M, Oshitari T, Kuwabara S, Yamamoto S. Correlation between peripapillary retinal thickness and serum level of vascular endothelial growth factor in patients with POEMS syndrome. *Br J Ophthalmol* 2015;100:897–901.
- [7] Doi S, Kimura S, Morizane Y, Hosogi M, Hosokawa M, Shiode Y, Kawata T, Kondo E, Shiraga F. POEMS syndrome in a 20-year-old patient diagnosed following a complaint of reduced visual acuity. *Acta Med Okayama* 2014;68:379–383.
- [8] Yokouchi H, Oshitari T, Baba T, Yamamoto S. Thalidomide reduces choroidal thickness and optic disc edema in a patient with POEMS syndrome. *Graefes Arch Clin Exp Ophthalmol* 2015;253:1195–1198.
- [9] Ecsedy M, Schneider M, Nemes J, Nemeth J, Recsan Z. Optical coherence tomography features of POEMS syndrome and Castleman disease-associated papillopathy. *Ocul Immunol Inflamm* 2014;22:454–460.
- [10] Dispenzieri A. POEMS syndrome: 2014 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2014;89:214–223.
- [11] Misawa S, Sato Y, Katayama K, Nagashima K, Aoyagi R, Sekiguchi Y, Sobue G, Koike H, Yabe I, Sasaki H, Watanabe O, Takashima H, Nishizawa M, Kawachi I, Kusunoki S, Mitsui Y, Kikuchi S, Nakashima I, Ikeda S I, Kohara N, Kanda T, Kira JI, Hanaoka H, Kuwabara S. Safety and efficacy of thalidomide in patients with POEMS syndrome: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2016;15:1129–1137.
- [12] Blade J, Cibeira MT, Rosinol L. Bortezomib: a valuable new antineoplastic strategy in multiple myeloma. *Acta Oncol* 2005;44:440–448.
- [13] Kaygusuz I, Tezcan H, Cetiner M, Kocakaya O, Uzay A, Bayik M. Bortezomib: a new therapeutic option for POEMS syndrome. *Eur J Haematol* 2010;84:175–177.
- [14] Kuwabara S, Misawa S, Kanai K, Kikkawa Y, Nishimura M, Nakaseko C, Cho RK, Hattori T. Autologous peripheral blood stem cell transplantation for POEMS syndrome. *Neurology* 2006;66:105–107.
- [15] Park B, Yoo KH, Kim C. Hematopoietic stem cell expansion and generation: the ways to make a breakthrough. *Blood Res* 2015;50:194–203.
- [16] Yokouchi H, Baba T, Misawa S, Sawai S, Beppu M, Kitahashi M, Oshitari T, Kuwabara S, Yamamoto S. Correlation between serum level of vascular endothelial growth factor and subfoveal choroidal thickness in patients with POEMS syndrome. *Graefes Arch Clin Exp Ophthalmol* 2015;253:1641–1646.
- [17] Yokouchi H, Baba T, Misawa S, Kitahashi M, Oshitari T, Kuwabara S, Yamamoto S. Changes in subfoveal choroidal thickness and reduction of serum levels of vascular endothelial growth factor in patients with POEMS syndrome. *Br J Ophthalmol* 2016 Oct 4. pii: bjophthalmol-2016-309319.

- [18] Hudson N, Powner MB, Sarker MH, Burgoyne T, Campbell M, Ockrim ZK, Martinelli R, Futter CE, Grant MB, Fraser PA, Shima DT, Greenwood J, Turowski P. Differential apicobasal VEGF signaling at vascular blood-neural barriers. *Dev Cell* 2014;30:541–552.
- [19] Tso MO, Shih CY, McLean IW. Is there a blood-brain barrier at the optic nerve head? *Arch Ophthalmol* 1975;93:815–825.
- [20] Song HB, Yu HG. Optic disc edema responding to localized anti-vascular endothelial growth factor treatment in a patient with POEMS syndrome. *Korean J Ophthalmol* 2015;29:357–358.
- [21] Misawa S, Sato Y, Katayama K, Hanaoka H, Sawai S, Beppu M, Nomura F, Shibuya K, Sekiguchi Y, Iwai Y, Watanabe K, Amino H, Ohwada C, Takeuchi M, Sakaida E, Nakaseko C, Kuwabara S. Vascular endothelial growth factor as a predictive marker for POEMS syndrome treatment response: retrospective cohort study. *BMJ Open* 2015;5:e009157.