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Vascular endothelial growth factor as a predictive marker for POEMS syndrome treatment response: retrospective cohort study

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ABSTRACT

Objective: POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome is a rare multisystem disease characterised by plasma cell dyscrasia and overproduction of vascular endothelial growth factor (VEGF). VEGF is assumed to be useful in monitoring disease activity, because VEGF levels usually decrease after treatment. However, there is no study to investigate whether the extent of decrease in VEGF correlates with clinical outcome. We tested the predictive efficacy of serum VEGF levels in POEMS syndrome.

Method: This was an institutional review board approved retrospective observational cohort study of 20 patients with POEMS monitored regularly for more than 12 months (median follow-up, 87 months) after treatment onset using our prospectively accumulated database of POEMS from 1999 to 2015. Patients were treated by autologous peripheral blood stem cell transplantation or thalidomide administration. Serum VEGF was measured by ELISA. Outcome measures included clinical and laboratory findings and relapse-free survival.

Results: Serum VEGF levels decreased rapidly after treatment, and stabilised by 6 months post treatment. Patients with normalised serum VEGF levels (<1040 pg/mL) at 6 months showed prolonged relapse-free survival (HR=12.81, 95% CI 2.691 to 90.96; p=0.0001) and greater later clinical improvement. The rate of serum VEGF reduction over the first 6 months post treatment correlated with increased grip strength, serum albumin levels, and compound muscle action potential amplitudes at 12 months.

Conclusions: Serum VEGF level at 6 months post treatment is a predicative biomarker for disease activity and prognosis in POEMS syndrome. Serum VEGF could be used as a surrogate endpoint for relapse-free survival or clinical or laboratory improvement of POEMS syndrome for clinical trials.

Strengths and limitations of this study

- This study showed the extent of serum vascular endothelial growth factor (VEGF) reduction after treatment significantly correlates with the prognosis in POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome.
- VEGF can be used as a surrogate marker in prospective clinical trials for POEMS syndrome.
- This is a retrospective study, including a small number of patients of different background and age.

INTRODUCTION

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome is a rare (prevalence 0.3 per 100 000) multisystemic disorder associated with plasma cell dyscrasia.[1 2] Potentially fatal clinical manifestations include progressive demyelinating polyneuropathy leading to tetraplegia.[3–5] Overproduction of vascular endothelial growth factor (VEGF), a multifunctional cytokine that induces angiogenesis and microvascular hyperpermeability,[6] may be involved in the pathogenesis of many POEMS symptoms. Serum VEGF is markedly and specifically elevated in this syndrome,[7–10] and major diagnostic criteria include increased VEGF.[11–13] Moreover, serum VEGF concentration usually decreases following successful therapeutic intervention.[14–17] However, no study has investigated whether changes in VEGF levels after treatment are predictive of clinical improvement or outcome.

New therapeutic interventions, such as autologous peripheral blood stem cell transplantation and immunomodulatory drug regimens, have improved POEMS prognosis,[14 15 18 19] but comparative evaluations of treatment efficacy are lacking. Most POEMS studies are retrospective case series or case reports rather than prospective randomised controlled clinical trials due to the rarity of

this disease.[12] A reliable early biomarker of long-term outcome could facilitate clinical trials even with a limited patient sample. Therefore, we examined whether VEGF levels are predictive of longer-term clinical improvement.

METHODS

Subjects

This observational study was approved by the institutional review board of Chiba University Graduate School of Medicine. The diagnosis of POEMS was established using the published criteria.[12] Study subjects for this retrospective cohort study were drawn from our database of 85 consecutive patients with POEMS (57 men) treated from 1999 to 2015. From this database, we identified 21 consecutive patients who started primary POEMS syndrome treatment, peripheral blood stem cell transplantation or thalidomide, during the 10-year period 1999–2009 because in 2010 we began an ongoing clinical trial of POEMS syndrome in which serum VEGF levels are blinded.

From the 21 patients, we excluded one patient treated with bevacizumab (anti-VEGF monoclonal antibody) because bevacizumab strongly suppresses VEGF levels for several months. In the 20 patients, VEGF levels were measured regularly (at least once every 3–6 months) for more than 1 year after transplantation or thalidomide treatment and the median follow-up period is 87 months (range 24–133 months). Clinical signs (performance status, overall neuropathy limitation scale and grip strength (sum of both hands)) and blood tests were checked at each visit and nerve conduction studies were performed every 3–6 months. Eight patients were pretreated with low to moderate dose steroids (n=7) or immunoglobulin (n=1) prior to transplantation or thalidomide. Clinical and laboratory profiles of the 20 patients are shown in table 1. Changes in serum VEGF levels after treatment were measured and correlations with clinical/laboratory findings, relapse-free survival and complete remission were calculated. We defined relapse as clinical deterioration attributable to POEMS syndrome, such as extravascular overload (oedema/effusions/ascites) or neuropathy, and censoring was defined as the last visit during the observation period. Complete remission was defined according to the International Myeloma Working Group criteria: negative immunofixation with disappearance of any plasma cytomas and >5% plasma cells in the bone marrow.[17 20] One author (SM) selected the patients from the database and reviewed medical records. YS, who was blinded to the clinical information, mainly performed statistical analysis.

Treatments for POEMS syndrome

Patients were treated with transplantation (n=12) or thalidomide and dexamethasone (n=8). Autologous peripheral blood stem cell collection was performed after mobilisation by subcutaneous granulocyte colony-stimulating factor with or without high-dose cyclophosphamide (2 g/m^2/day for 2 consecutive days). High-dose melphalan chemotherapy (140–200 mg/m^2) and stem-cell transplantation were performed approximately 1 month after blood cell collection according to the standard treatment regimen for multiple myeloma. Melphalan dose was reduced in patients with performance status 4 (completely disabled). The median follow-up period after transplantation was 90 months (range 35–133 months). Combination thalidomide (100–300 mg/day on days 1–28) and dexamethasone (12 mg/m^2 on days 1–4) was administered every 4 weeks for 19–42 cycles (median 32 cycles). The median follow-up period after thalidomide administration was 87 months (range 24–106 months).

VEGF measurements

Serum VEGF levels were measured by ELISA commercially (Special Reference Laboratory Co., Tokyo, Japan).

Table 1 Patient characteristics (n=20)

	Auto-PBSCT (n=12)	Thalidomide (n=8)
Clinical profiles		
Age (years)	48 (36–61)	69 (59–84)
Gender (male:female)	9:3	5:3
Time from symptoms to therapy (months)	17 (2–120)	25 (4–101)
Performance status	1 (1–4)	2 (1–3)
Overall Neuropathy Limitation Scale	5 (1–11)	6 (2–9)
Laboratory data		
Albumin (g/dL)	3.8 (2.7–4.5)	3.4 (2.7–3.9)
Creatinine (mg/dL)	0.7 (0.5–1.2)	0.9 (0.4–2.0)
Immunoglobulin (IgA:IgG)	4:6	2:5
Vascular endothelial growth factor	2950 (126–7870)	2520 (1430–7970)
Nerve conduction study (median nerve)		
CMAP amplitude (mV)	5.3 (0–12.8)	5.2 (0.1–9.4)
Motor conduction velocity (m/s)	33.0 (23–45)	26 (14–48)

Data are given as median (range).
CMAP, compound muscle action potential; PBSCT, peripheral blood stem cell transplantation.

The cut-off values for diagnosis of POEMS was established using data from 50 untreated patients with POEMS (33 men; age range 34–76 years) from our retrospective cohort and samples from 120 healthy subjects (61 men; age range 21–79 years). The cut-off value for diagnosis (1040 pg/mL) was defined as the point with 100% sensitivity and 99% specificity by plotting receiver operating characteristic curves.

Statistical analyses

For the baseline variables, summary statistics were constructed employing frequencies and proportions for categorical data, and means and SDs for continuous variables. Univariate analyses were carried out using the t test or Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. For time-to-event outcomes, the Kaplan–Meier method was used to estimate relapse-free survival for each group, and the difference in survival between groups was compared by the log-rank test. The HRs and 95% CIs were estimated by the Cox proportional hazards model.

All comparisons were planned and the tests were two sided. A p value of less than 0.05 was considered to indicate a statistically significant difference. All statistical analyses were conducted using JMP, Japanese V.5.1.1 for Windows (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Changes in VEGF levels after treatment and relapse-free survival

Before the start of autologous peripheral blood stem cell transplantation or thalidomide treatment for POEMS syndrome, serum VEGF was elevated above the cut-off value (1040 pg/mL) in all but one patient. The one pretreated for 6 months with moderate-dose steroid (prednisone 20–30 mg daily) exhibited low VEGF levels throughout the study period following primary POEMS syndrome treatment (transplantation). Serum VEGF levels decreased steadily over 6 months after primary treatment and eventually stabilised in all patients (figure 1). Patients treated by transplantation (n=12) had a mean ±SD baseline VEGF of 3186±2072 pg/mL, decreasing to 668±481 pg/mL at 3 months, 664±584 pg/mL at 6 months, and 541±635 pg/mL at 12 months post treatment. The rate of decrease among patients treated with transplantation was steeper than those treated with thalidomide (3273±2244 pg/mL at baseline, 1770±1352 pg/mL at 3 months, 1223±857 pg/mL at 6 months, and 1350 ±993 pg/mL at 12 months). All patients with serum VEGF≥1040 pg/mL (cut-off value) at 6 months post treatment relapsed with a median time of 36 months. The Kaplan–Meier estimates of relapse-free survival at 3 years were 93% in patients with VEGF levels <1040 pg/mL and 40% in patients with VEGF levels ≥1040 pg/mL

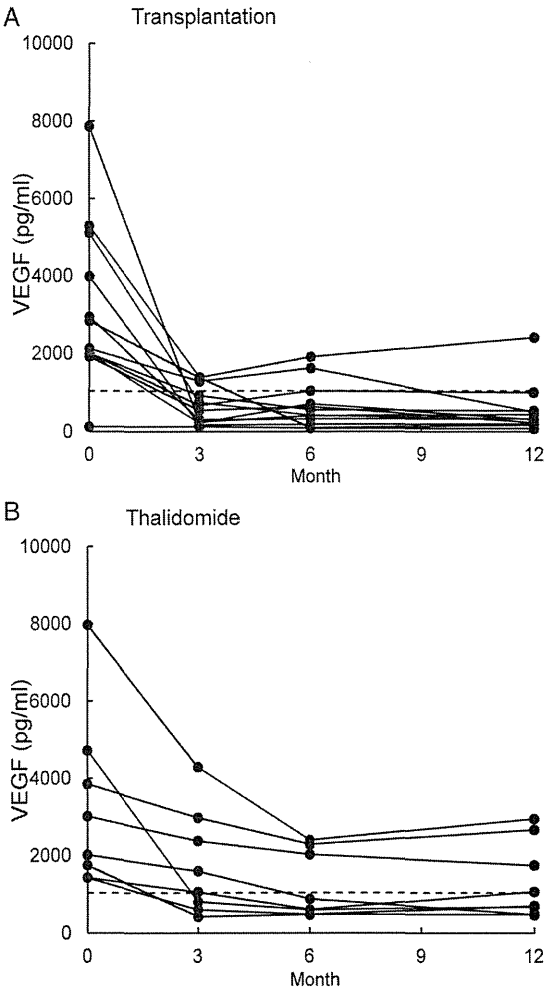

Figure 1 Changes in serum vascular endothelial growth factor (VEGF) after treatment. (A) Autologus peripheral blood stem cell transplantation with high-dose chemotherapy (n=12). (B) Thalidomide–dexamethasone therapy (n=8).

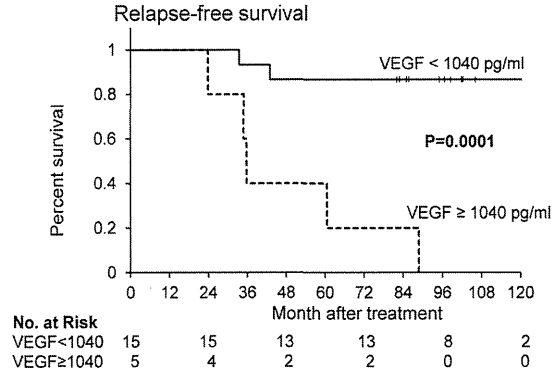

Figure 2 Kaplan–Meier plot for relapse-free survival. Patients with vascular endothelial growth factor (VEGF) <1040 pg/mL at 6 months after treatment showed significant longer relapse-free survival than patients with VEGF≥1040 pg/mL (HR=12.81, 95% CI 2.691 to 90.96; p=0.0001).

Table 2 Changes in clinical and laboratory parameters after treatment (n=20)

	A Baseline	B 6 months	C 12 months	p Value A vs B	p Value A vs C
Performance status	1.5 (1–4)	1 (1–4)	1 (1–4)	1.0	0.19
Overall Neuropathy Limitation Scale					
Arm scale	2 (0–4)	2 (0–4)	1 (0–4)	0.069	0.0016
Leg scale	3 (1–7)	3 (1–7)	2.5 (0–7)	0.15	0.025
Grip	28 (6–85)	32 (0–93)	40 (0–107)	0.052	0.014
Laboratory data					
Albumin (g/dL)	3.8 (2.7–4.5)	3.55 (2.7–4.8)	4.3 (2.7–5.1)	0.056	0.013
Creatinine (mg/dL)	0.77 (0.42–2.02)	0.77 (0.37–1.13)	0.84 (0.38–1.63)	0.13	0.44
Nerve conduction study (median nerve)					
CMAP amplitude (mV)	5.3 (0–12.8)	6.2 (0–14.1)	8.2 (0–4.6)	0.31	0.0005
Motor conduction velocity (m/s)	32 (17–48)	39 (20–50)	39 (20–50)	0.19	0.008

Data are given as median (range).
CMAP, compound muscle action potential.

at 6 months post treatment (HR=12.81; 95% CI 2.691 to 90.96; p=0.0001, figure 2). These findings suggest that suppression of serum VEGF levels to within the normal range at 6 months post treatment may prolong relapse-free survival. All of the seven patients with relapsed disease were treated with thalidomide. The complete remission rate did not differ significantly between the two groups.

VEGF reduction and clinical improvement

Significant clinical and laboratory improvement could not be detected at 6 months post treatment. However, at 12 months multiple clinical and laboratory parameters significantly improved (table 2). The extent of improvement in grip strength, serum albumin and compound muscle action potential amplitude of the median nerve were significantly greater in patients with VEGF levels <1040 pg/mL than in patients with serum VEGF ≥1040 pg/mL at 6 months post treatment (figure 3). In addition, rate of decrease over the first 6 months post treatment was correlated with the extent of clinical and laboratory improvements at 12 months (figure 4). These findings suggest that significant clinical and laboratory improvement can be obtained several months after VEGF levels decrease, and that the greater the decrease by 6 months post treatment, the greater the delayed improvement in laboratory findings and clinical outcome. No significant correlations between decreases in VEGF and improvement in performance status, overall neuropathy limitation scale, pleural effusion or creatinine could be detected.

DISCUSSION

We show that serum VEGF levels decreased and reached a plateau over the 6 months following treatment of peripheral blood stem cell transplantation or thalidomide. Patients with normal VEGF levels at 6 months post treatment showed significantly longer relapse-free survival and greater delayed clinical and laboratory improvements. The rate of reduction in serum VEGF over the first 6 months after treatment correlated with the extent of clinical and laboratory improvement at 12 months. These findings suggest that the extent of reduction in VEGF correlates with improvement of the disease and treatments for POEMS syndrome should aim to decrease serum VEGF within the normal range. In addition, the fact that decreased serum VEGF reached a plateau over 6 months after treatment indicates that at least 6 months are required to determine the effect of treatment, and a change in therapeutic strategy should be considered if VEGF levels do not decrease sufficiently at 6 months post treatment. This is the first study to demonstrate that serum VEGF level can be used as a surrogate biomarker to monitor disease activity and predict clinical outcome of POEMS syndrome. A reliable early predictive marker of long-term outcome will facilitate clinical trials for POEMS syndrome treatment given the inherent difficulty in larger scale prospective studies for such rare and severe diseases.

Since the first demonstration of elevated serum VEGF levels in POEMS syndrome patients,[7] numerous studies have confirmed that VEGF levels increase in untreated POEMS syndrome and decrease after treatment, implicating elevated VEGF in disease pathophysiology.[14–19] Indeed, the physiological effects of VEGF, such as vascular hyperpermeability and angiogenesis,[6] are consistent with the characteristic symptoms of POEMS syndrome (eg, pleural effusion, oedema or angiomata). However, whether lower VEGF levels after treatment represent suppression of the disease itself or a mere epiphenomenon had not been unequivocally demonstrated. The present study clearly shows that the extent of the decreases in VEGF reflects later clinical improvement; a greater reduction at 6 months post treatment predicts better prognosis at 1 year. Moreover, if VEGF levels are suppressed below the upper limit of the normal range, longer remission can be achieved. Therefore, treatment for POEMS should aim to control VEGF within the

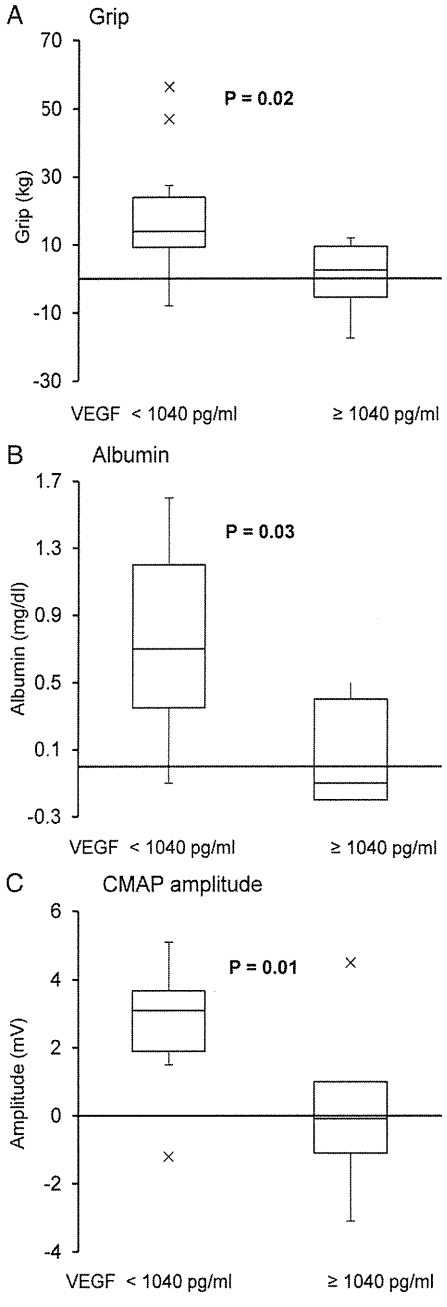

Figure 3 Changes in clinical or laboratory measures at 12 months post treatment. (A) Grip strength. (B) Serum albumin. (C) Compound muscle action potential (CMAP) amplitude of the median nerve. Patients with serum vascular endothelial growth factor (VEGF) <1040 pg/mL at 6 months after treatment showed significant improvements in all parameters compared with patients with VEGF ≥1040 pg/mL.

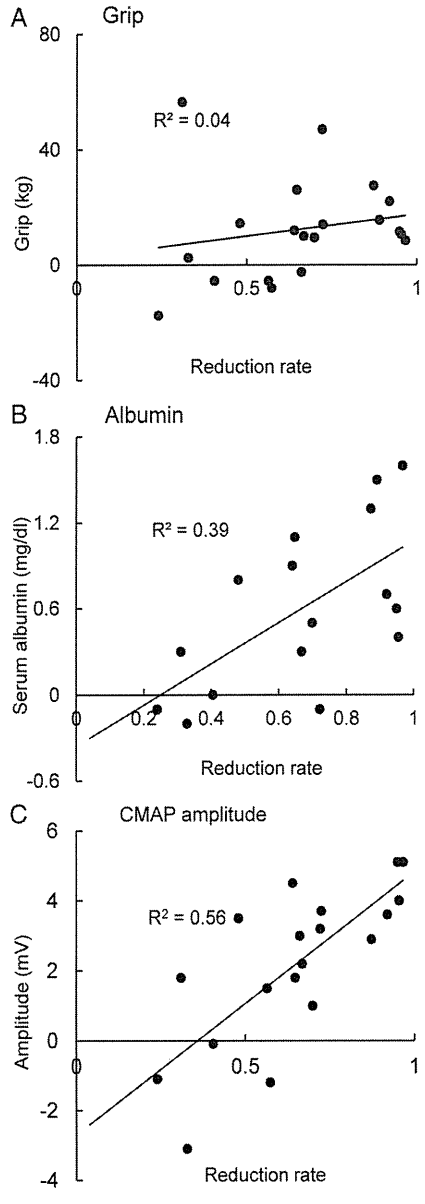

Figure 4 Correlation between reduction rate of vascular endothelial growth factor (VEGF) at 6 months after treatment and changes in grip strength (A), serum albumin (B), and CMAP amplitude of the median nerve (C) at 12 months after treatment. The grater the rate of VEGF decline at 6 months of treatment, the better the clinical and laboratory findings at 12 months.

normal range. These findings strongly suggest that overproduction of VEGF plays a central role in the pathophysiology of POEMS syndrome.

This retrospective study has several limitations. First, we retrospectively investigated a small number of patients with POEMS with different backgrounds. The difference in mean age of the two groups of studied patients (transplanted and thalidomide treated) may substantially influence treatment response and VEGF level. However, we aimed to study whether VEGF could be used as a predictive marker, irrespective of the patients' background and treatment modality. We believe that this was achieved by our data. Second, we investigated whether only serum VEGF levels reflect disease activity and prognosis of POEMS syndrome, or whether other proinflammatory cytokines, such as TNF-α, IL-6 and IL-12, are also upregulated during active disease and IL-12 levels decrease after treatment.[21]

Inhibition of VEGF alone by a monoclonal antibody (bevacizumab) does not appear to be effective, particularly in advanced cases,[22–24] further implicating other proinflammatory factors in disease progression. Future prospective studies are necessary to investigate which cytokines are most appropriate for monitoring disease activity. Third, the present study evaluated serum levels of VEGF, and it is controversial whether serum or plasma VEGF is a better indicator of disease activity.[11 17 25] While plasma level of VEGF is less affected by platelets, serum VEGF levels can be reflected from the serous and platelet compartments. Since the origin of VEGF in POEMS syndrome has not yet been clarified, VEGF stored in platelets may play an important role in the pathophysiology of POEMS syndrome. Therefore, we consider that monitoring serum VEGF may better indicate the total amount of VEGF in the patient.[26] However, further investigations may be required to evaluate the relationship between serum and plasma VEGF levels in the treatment course of POEMS syndrome.

The prognosis for patients with POEMS syndrome was very poor when only corticosteroids were available as treatments.[3 4] However, a number of case series and reports have demonstrated improved prognosis using treatments originally developed for multiple myeloma.[12 14 15 18 19] The next step is to perform well designed prospective clinical trials and establish evidence-based therapeutic guidelines.[12 13] To confirm the efficacy of a therapeutic intervention, so-called hard endpoints are expected, such as overall survival or progression-free survival. However, such studies take several years and require large sample sizes,[11 27] and are generally not feasible for rare diseases. Surrogate endpoints to assess therapeutic efficacy in a brief period could allow short-term clinical trials involving smaller patient groups. This study demonstrates that serum VEGF at 6 months post treatment can be used as a primary endpoint for POEMS syndrome treatment outcome. In addition, VEGF is suitable for an endpoint of clinical trials from the view point that VEGF measurement is quantitative and objective and can be blinded by measurement at a central laboratory.

Additional agents for multiple myeloma, such as proteasome inhibitors, monoclonal antibodies, cell cycle specific drugs, deacetylase inhibitors and signalling transduction pathway inhibitors will be available in the near future[28] and could be applied to POEMS syndrome.[13] While the adequacy of serum VEGF as a surrogate endpoint needs further confirmation, this marker may facilitate prospective clinical trials on the safety and efficacy of these newer drugs despite the rarity of this syndrome. In fact, we are now conducting a multicentre, double-blind and randomised controlled clinical trial[29] to evaluate the efficacy and safety of thalidomide for POEMS syndrome using the rate of VEGF decrease over 6 months post treatment as the primary endpoint (declared and registered to the Japan Pharmaceuticals and Medical Devices Agency).

Contributors SM and YS analysed the data. SM, YS, KK, HH and SK designed the research, collected and wrote the manuscript. SS, MB, FN, KS, YS, YI, KW, HA, CO, MT, ES and CN assisted in data collection and manuscript preparation. All authors approved the final draft of the paper.

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Ethics approval The protocol was approved by the institutional review board of Chiba University Graduate School of Medicine.

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Acutely deteriorated extravascular volume overload during peripheral blood stem cell mobilization in POEMS syndrome: A case series with cytokine analysis

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Case Report

Acutely deteriorated extravascular volume overload during peripheral blood stem cell mobilization in POEMS syndrome: A case series with cytokine analysis

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Cytokine profile

ABSTRACT

We describe two cases of polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome patients with deteriorated extravascular volume overload without increased levels of vascular endothelial growth factor after the administration of cyclophosphamide + granulocyte colony-stimulating factor for stem cell mobilization. We then measured the serum levels of 27 cytokines from these cases using a multiplex suspension array system. The analysis revealed the changes of cytokine profiles before cyclophosphamide + granulocyte colony-stimulating factor and after the development of capillary leak symptoms in both cases. This may improve our current level of understanding of the pathogenesis of POEMS syndrome not driven by vascular endothelial growth factor.

1. Introduction

Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome is a rare plasma cell disorder characterized by the constituent ailments that comprise its name. Signs of extravascular volume overload, which are frequently observed in POEMS syndrome, are among the most common preterminal events in POEMS syndrome [1]. It has been speculated that elevated levels of vascular endothelial growth factor (VEGF) play a crucial role in inducing extravascular volume overload via angiogenesis and microvascular hyperpermeability [1,2]. However, discrepancies between disease activity and VEGF levels in POEMS syndrome patients have been reported [3]. Additionally, the efficacy of the anti-VEGF monoclonal antibody bevacizumab for POEMS syndrome patients has been a matter of controversy due to mixed study results [4–6]. Furthermore, several other cytokines, such as interleukin (IL)-6, IL-12, tumor necrosis factor-α, and hepatocyte growth factor, have been reported to be elevated in POEMS syndrome [7–9]. Therefore, VEGF may not be the driving force behind this disorder. Here we report two cases of patients with POEMS syndrome with acutely deteriorated extravascular volume overload without increased levels of VEGF after

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the administration of high dose cyclophosphamide (HD-CY) + granulocyte colony-stimulating factor (G-CSF) (CG) for peripheral blood stem cell (PBSC) mobilization. We then measured serum levels of 27 cytokines from these cases before and after CG using a multiplex suspension array system, and analyzed the changes in their cytokine profiles during their clinical courses.

2. Case 1

The first case (case 1) is a 61-year-old man who was diagnosed with POEMS syndrome and was referred to our institution in July 2008. His clinical course is shown in Fig. 1. The day of administration of G-CSF for PBSC collection is defined as day 0. The patient presented with monoclonal gammopathy (IgG-λ), a slight left pleural effusion, hepatosplenomegaly, and polyneuropathy with a performance status of 2. The level of serum VEGF was 8160 pg/mL on day minus 29. He was treated with high-dose dexamethasone (DEX: 40 mg/body; days minus 21 to minus 18), leading to an improvement in his systemic edema. He received HD-CY (2 g/m^2; days minus 13 to minus 12), followed by G-CSF (10 μg/kg; days 0–4) for PBSC collection. PBSC collection was performed on day 4. The required number of CD34$^+$ cells (5.12×10^6/kg) for autologous stem cell transplantation were harvested using the COBE Spectra cell separator (COBE Spectra, CaridianBCT, USA), although respiratory failure occurred 3 days after PBSC collection, and a computed

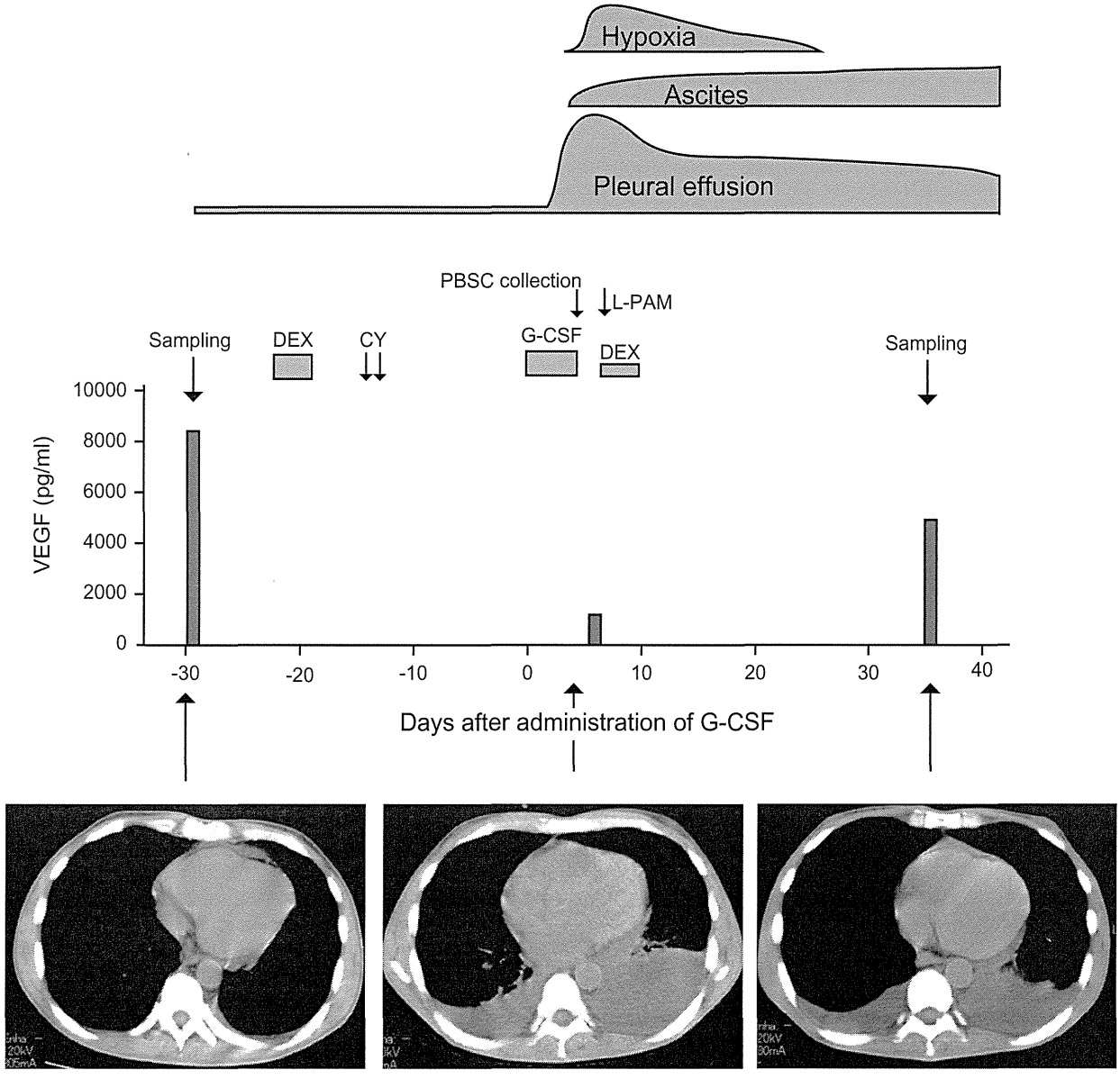

Fig. 1. Serial changes in computed tomography (CT) scan images and vascular endothelial growth factor (VEGF) level, and the therapeutic course of case 1. The sera sampling time points for the multiplex suspension array system are indicated by arrows. DEX, dexamethasone; CY, cyclosphosphamide; PBSC, peripheral blood stem cell; L-PAM, melphalan.

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tomography (CT) scan revealed a massive pleural effusion and ascites. Additional treatment with melphalan (20 mg/m^2; day 7), and dexamethasone (20 mg/kg; days 7–10), was administered. Notably, the level of serum VEGF at the time of PBSC collection was reduced to 1210 pg/mL. Although the patient became oxygen-free after the treatment, a considerable volume of pleural effusion and ascites remained. In addition, the level of serum VEGF was increased to 4770 pg/mL on day 35 after the administration of G-CSF. Autologous stem cell transplantation was performed on day 39. The patient developed a sudden cardiopulmonary arrest with an unknown cause on day 85, and died on day 91 after the administration of G-CSF for PBSC collection.

3. Case 2

The second case (case 2) is a 64-year-old woman who was diagnosed with POEMS syndrome with monoclonal gammopathy (IgG-λ), polyneuropathy, a left pleural effusion, and pericardial effusion at a different hospital in October 2005. She was suffering from refractory pleural effusion after receiving 2 courses of steroid-pulse therapy and melphalan (4 mg/day × 4 days) + prednisolone (20 mg/day × 4 days) therapy, and was referred to our hospital in September 2009. Her clinical course is shown in Fig. 2. The day of administration of G-CSF for second attempt of PBSC collection is defined as day 0. The patient presented with systemic edema, left pleural effusion, pericardial effusion, and polyneuropathy. Her serum VEGF level on day minus 163 was 1360 pg/mL and her performance status was 3. Thalidomide monotherapy of 100 mg/day facilitated a slight improvement in the extravascular volume overload, and the patient's serum VEGF level was decreased to 883 pg/mL on day minus 122. She underwent PBSC collection by G-CSF alone using the COBE Spectra cell separator on day minus 94, although the number of CD34$^+$ cells was insufficient. Because serum VEGF level was increased to 2540 pg/mL on day minus 70, 3 courses of additional thalidomide (200 mg/day × 28 days) + DEX (12 mg/m^2/day × 4 days) therapy were performed. Serum VEGF level was mildly reduced to 1850 pg/mL on day minus 30, and the patient received HD-CY (CY: 2 g/m^2; days minus 11 to minus 10), followed by G-CSF (10 μg/kg; days 0–2) for PBSC collection. On day 3, she developed fever, hypoxia, acute renal failure, and hypotension, and CT scan revealed a deteriorated pleural and pericardial effusion. Mechanical ventilation and continuous hemodiafiltration in the intensive care unit (ICU) were required to support her life. Her serum VEGF level was reduced to 117 pg/mL, while her serum IL-6 level increased to 63.0 pg/mL on day 3. PBSC collection was cancelled because of her life-threatening condition, and additional treatment with thalidomide (100 mg/day) and DEX (40 mg/day; days 5–8) was initiated. Her respiratory distress and acute renal failure improved after the treatment,

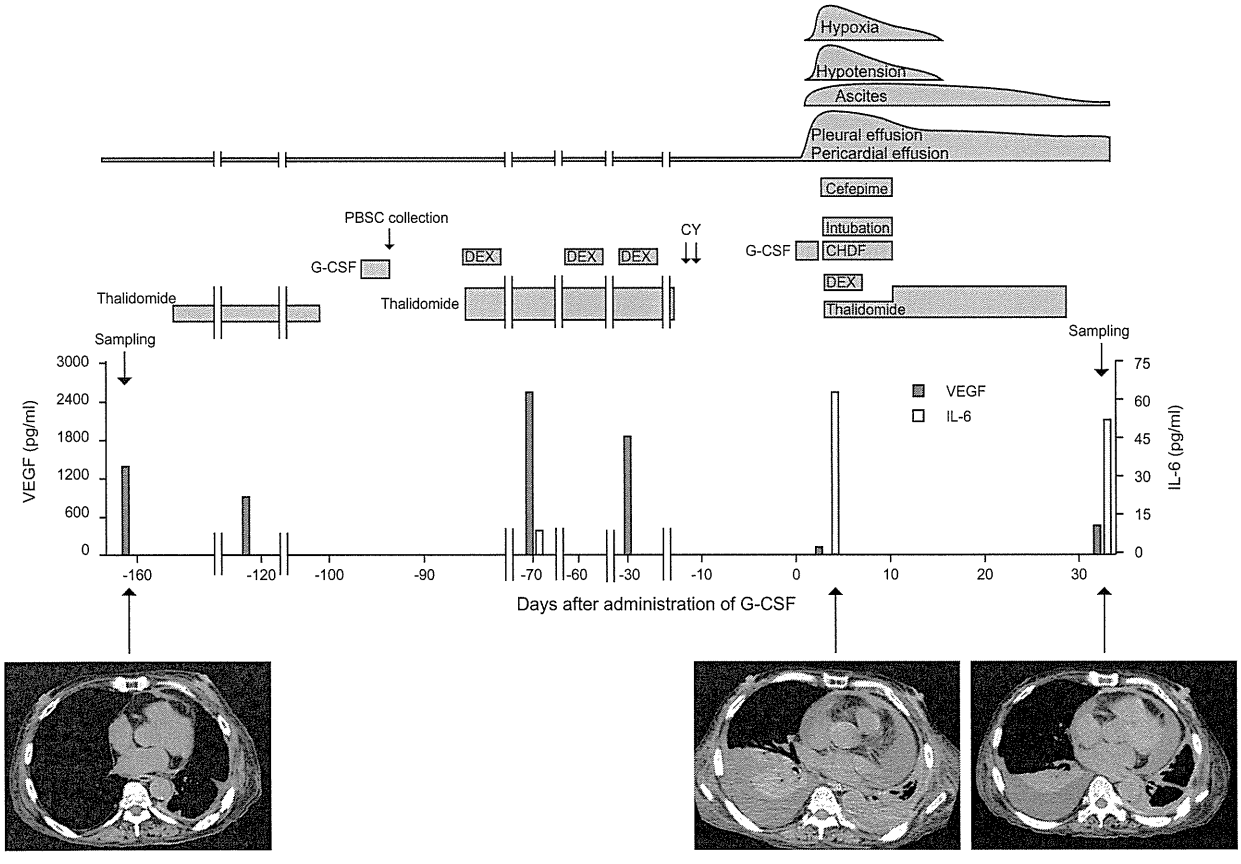

Fig. 2. Serial changes in CT scan images and cytokine levels, and the therapeutic course of case 2. IL-6, interleukin-6; CHDF, continuous hemodiafiltration.

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and she was discharged from the ICU on day 11 after the administration of G-CSF. Despite the continuation of the treatment by thalidomide monotherapy (200 mg/day), pleural and pericardial effusion still remained on day 33. Serum levels of IL-6 and VEGF also remained elevated and reduced, respectively (51.2 pg/mL and 453 pg/mL, respectively). She was transferred to a hospital closer to her hometown on day 137 after the administration of G-CSF.

4. Cytokine analysis

The serum concentrations of 27 cytokines and chemokines from these two cases were measured using a multiplex suspension array system (Table 1). The sera in case 1 were obtained 29 days before and 35 days after the administration of G-CSF for PBSC collection (Fig. 1). The sera in case 2 were obtained 163 days before and 33 days after the administration of G-CSF for second attempt of PBSC collection (Fig. 2). Sera from normal controls were obtained from people without malignancies at medical check-ups after informed consent was obtained. The average age of normal controls (n = 20) was 57.4 years. We defined the upper and lower limits of normal for each cytokine as the mean ± 3 standard deviations of normal control values in the same manner as our previous study [8]. The study was approved by the Ethics Committee of the Chiba University School of Medicine, and we received consent from each patient. In case 1, the levels of five cytokines, including IL-6, were elevated after CG (black colors in Table 1). The levels of four cytokines, including VEGF, were decreased, but remained abnormally high after CG (pale gray color in Table 1), while the abnormally high levels of two cytokines (IL-13 and monocyte chemotactic protein–1) were decreased to normal levels after CG. In case 2, the abnormally high levels of three cytokines (IL-10, IL-12, and VEGF) were decreased to normal levels after CG, while the level of IL-6 was increased to an abnormally high level after CG (black color in Table 1).

5. Discussion

To our knowledge, this is the first analysis of cytokine profiles in POEMS syndrome patients who developed acutely deteriorated extravascular volume overload. The development of capillary leak symptoms without increased levels of VEGF prompted us to speculate that the cytokine profiles in our cases may be altered after the administration of CG. Although the cytokine profiles of two patients in this study were different, it is noteworthy that levels of IL-6 after CG were elevated in both cases. IL-6 is a proinflammatory cytokine involved in pathogenesis of various diseases,

Table 1
Serum cytokine levels[a] in control samples and POEMS syndrome patients with severe capillary leak symptoms.

	Control (n = 20)			Case 1			Case 2		
	Mean	SD	Mean + 3SDs	Before	After	Fold change (before/after)	Before	After	Fold change (before/after)
VEGF	134	76.6	363	3593	1753	0.49	564	107	0.19
IL-12 (p70)	82	42.7	210	797	510	0.64	224	51.6	0.23
IL-10	19.2	10.6	51	132	109	0.83	55	9.3	0.17
IL-7	11.1	3.7	22.4	51.3	31.8	0.62	16.3	6.9	0.42
MCP-1	45.7	15.2	91.4	103	47.7	0.46	78.7	23.9	0.30
IL-13	15	4.8	29.4	32.9	24	0.73	16.1	7.1	0.44
IL-8	24.7	12.6	62.4	165	380	2.30	32.7	27.7	0.85
MIP-1β	438	225	1112	1209	2478	2.05	481	332	0.69
IL-6	8	3.6	18.9	16.6	45	2.71	8.6	30	3.49
MIP-1α	9.2	8.3	34.1	32.6	100	3.07	5.4	3.8	0.70
IL-1β	2	0.82	4.4	4.3	7.5	1.74	1.6	0.68	0.43
IL-1ra	114	95.3	400	214	102	0.48	94	16.9	0.18
IL-2	3.7	5.2	19.1	ND	ND	–	ND	ND	–
IL-4	5.1	1.3	8.9	6.9	3.9	0.57	4.4	3.8	0.86
IL-5	2.3	1.2	6	3.6	2.1	0.58	1.5	ND	–
IL-9	31.2	50.5	182	42.5	33.3	0.78	18.6	8.8	0.47
IL-15	ND			ND	ND	–	ND	ND	–
IL-17	25.8	23.4	96	47.3	10.6	0.22	20	ND	–
Eotaxin	77.2	35.7	184	62.2	54.2	0.87	138	60	0.43
FGF basic	42.9	24.5	116	72.2	27.9	0.39	63.9	10.2	0.16
G-CSF	60.3	28.2	145	114	68.9	0.60	53.5	22.8	0.43
GM-CSF	13	31.1	106	27.4	6.9	0.25	ND	ND	–
IFN-γ	66.7	23.4	136	120	64.4	0.54	48.8	25.8	0.53
IP-10	1643	1808	7067	1813	3388	1.87	6298	6730	1.07
PDGF-BB	759	240	1479	853	348	0.41	381	400	1.05
TNF-α	44.4	26.3	123	65.3	118	1.81	38.5	78.5	2.04
RANTES	12363	1183	8814[b]	8877	6127	0.69	8738	9268	1.06

Serum cytokine levels of control samples and POEMS syndrome patients before and after cyclophosphamide (CY) and G-CSF (CG) were administered. Gray colors represent the cytokines with abnormally high levels before CG. Pale gray colors represent the cytokines with reduced levels after CY, but still in the abnormal range. Black colors represent the cytokines with elevated levels after CY as compared to those before CY, and in the abnormal range. [a]pg/mL; [b]Mean-3SD. FGF, fibroblast growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; IL-1ra, interleukin-1 receptor antagonist; IP, induced protein; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; PDGF, platelet-derived growth factor; RANTES, regulated upon activation, normal T cell expressed and secreted; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; ND, not detected.

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including multiple myeloma and Castleman's disease [10]. In addition, the level of IL-6 is also frequently elevated in POEMS syndrome patients [11]. Thus, IL-6 might play an important role of developing capillary leak symptoms after CG in both cases. Other cytokines with changed levels before and after CG in the present study are also informative. For instance, the level of inflammatory protein (MIP)-1α in case 1 was increased to abnormally high level after CG. MIP-1α has been reported to be a key proinflammatory cytokine in the pathogenesis of inflammatory diseases, such as multiple sclerosis [12]. Additionally, the ratio of IL-1β to IL-1 receptor antagonist (IL-1ra) was increased after CG. In fact, the results of previous studies have implicated an imbalance of IL-1β and IL-1ra as a contributing factor in several inflammatory diseases [13,14]. Thus, elevated level of MIP-1α and an increased ratio of IL-1β to IL-1ra may contribute to the acutely deteriorated extravascular volume overload after CG as well as elevated level of IL-6 in case 1.

The factor that induced the change of the cytokine profile, leading to acutely deteriorated extravascular volume overload observed in this study, is crucial. It has been speculated that the use of G-CSF in POEMS syndrome patients may increase the release of proinflammatory cytokines and lead to worsened clinical symptoms [15,16]. In addition, POEMS syndrome is known to have high rates of engraftment syndrome after autologous stem cell transplantation [17]. As exaggerated cytokine responses during marrow reconstitution after autologous stem cell transplantation are suspected to contribute to developing engraftment syndrome, an overlap in mechanism of exaggerated production of proinflammatory cytokines between the clinical symptoms in our cases and engraftment syndrome may exist. Indeed, the level of IL-6, which is considered an important factor of engraftment syndrome [18], was increased after CG in both cases in this study. Taken together, G-CSF and hematological recovery from bone marrow suppression induced by HD-CY might cooperate to increase the release of proinflammatory cytokines, resulting in developing capillary leak symptoms in our cases.

Other than exaggerated production of proinflammatory cytokines described above, the reduction of VEGF level may play some role of the deteriorated extravascular volume overload in our cases. VEGF is an important survival factor for newly formed blood vessels. Of note, removing VEGF leads to apoptosis of endothelial cells [19,20]. Therefore, it is speculated that sudden VEGF removal may induce sudden collapse of a newly formed fragile vessels and an increase of capillary leakiness [6,21]. Remarkable reduction of VEGF levels by HD-CY in the present cases might also contribute to microvascular hyperpermeability.

The current study has some limitations. The number of patients is small, and the treatments for capillary leak symptoms after the administration of CG probably affect the results of multiplex suspension array system. In addition, it is an important issue how our findings in this study should be applied to understand the pathogenesis of POEMS syndrome not via VEGF. Thus, a future study on a large scale using sera at appropriate timings from POEMS syndrome patients who develop capillary leak symptoms without increased VEGF levels, such as a relapsed patient after autologous stem cell transplantation, should be performed [22]. Despite these limitations, our findings indicated that exaggerated production of proinflammatory cytokines may have contributed to acutely deteriorated extravascular volume overload during stem cell mobilization, which may improve our understanding of the pathogenesis of POEMS syndrome not attributable to VEGF.

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Correlation between peripapillary retinal thickness and serum level of vascular endothelial growth factor in patients with POEMS syndrome.
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Correlation between peripapillary retinal thickness and serum level of vascular endothelial growth factor in patients with POEMS syndrome

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ABSTRACT

Aims To determine whether there is a significant correlation between the peripapillary retinal thickness (pRT) and the serum level of vascular endothelial growth factor (VEGF) in patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome.

Methods This was a cross-sectional, observational case series. We studied 34 eyes of 17 treatment-naïve patients with POEMS syndrome whose intracranial pressure was within the normal range. The spectral-domain optical coherence tomographic (SD-OCT) examinations consisted of circle scans of 3.45 mm diameter around the optic disc. The pRT was automatically measured in the SD-OCT images and was used for the statistical analysis. The serum level of VEGF was measured by ELISAs, and the correlation between the pRT and the serum level of VEGF was determined. Multivariable logistic regression analyses were used to identify independent factors that were correlated with the pRT.

Results There was a significant positive correlation between the serum levels of VEGF and the average pRT of the two eyes of each patient ($r=0.81$, $p<0.0001$). There was a significant correlation between the pRT of the right and left eyes with an intraclass correlation coefficient of 0.839. Multiple regression analysis showed that the serum levels of VEGF were independent contributors to the pRT (standard regression coefficient=0.59, $p=0.012$).

Conclusions The significant correlation between the pRT and the serum level of VEGF suggests that the higher serum level of VEGF might be associated with the development of the optic disc oedema in patients with POEMS syndrome.

INTRODUCTION

Patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes are diagnosed with POEMS syndrome, and they are associated with plasma cell dyscrasia.[1] The overproduction of vascular endothelial growth factor (VEGF) has been suggested to be the cause of POEMS syndrome, although the pathogenesis has not been determined definitively. VEGF promotes neovascularisation and enhances vascular permeability,[1–3] and these alterations have been suggested to be responsible for the signs of POEMS syndrome, such as oedema, angiomata, organomegaly and pleural effusion/ascites.[2]

The pathogenesis of the ocular abnormalities associated with POEMS syndrome has not been determined, and data on the incidence and spectrum of these associations are limited. The major ocular finding in POEMS syndrome is optic disc oedema (ODO) as reported in several single case reports and small case series.[1 4–8] It has been suggested that an elevated VEGF level or elevated intracranial pressure (ICP) might play a role in the development of ODO.[4 7–11]

Optical coherence tomography (OCT) is a non-invasive imaging technique producing high-resolution cross-sectional images of the retina. The retinal thickness measurements obtained by OCT have been used mainly to evaluate macular oedema, and the measurements are accurate for the distance between the internal limiting membrane (ILM) and retinal pigment epithelium (RPE). In addition, the measurements are useful for evaluating oedema in the peripapillary region. The peripapillary thickness measurements by OCT have been used to evaluate the optic disc in patients with idiopathic intracranial hypertension,[12] and the total peripapillary thickness has also been used to diagnose papilloedema.[13 14]

The purpose of this study was to determine whether the peripapillary retinal thickness (pRT) in patients with POEMS syndrome with normal ICP was significantly correlated with the serum level of VEGF.

MATERIALS AND METHODS

We reviewed the medical records of 34 eyes of 17 treatment-naïve patients with the POEMS syndrome at the Chiba University Hospital from September 2013 to March 2015. The diagnosis of POEMS syndrome was made according to published criteria in 2013.[15]

The design and protocol of this study was approved by the Institutional Review Board of Chiba University Graduate School of Medicine. All procedures conformed to the tenets of the Declaration of Helsinki, and patients were informed about the aim of the study, and written consents were obtained.

Patients were excluded if even one eye had: an axial length >26.5 mm, intraocular pressure (IOP) >21 mm Hg, history of intraocular surgery, history of retinal or choroidal vascular diseases and glaucoma. In addition, patients were excluded if the opening lumbar puncture (LP) pressure was >20 cm H_2O. Cranial CT and MRI did not find any intracranial pathology or optic nerve infiltration in any of the patients.

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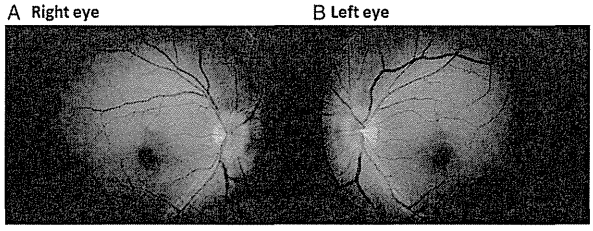

Figure 1 Ocular findings in a patient with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome (case 8). Fundus photographs showing bilateral optic disc oedema; (A) right eye, (B) left eye.

Dilated ophthalmoscopy was performed by one experienced neuro-ophthalmologist (TO) using a 90-diopter lens.[16] ODO was diagnosed when one of the following was present: hyperaemia of the disc, disc blurring, or absence of spontaneous venous pulsations[16] (figure 1A, B).

The data collected from all patients included the best-corrected visual acuity (BCVA) measured with a Snellen chart, IOP, axial length, slit lamp biomicroscopy and ophthalmoscopic findings. Blood samples were collected from all of the patients, and the opening LP pressure was measured. The major outcomes were the pRT thickness and the serum level of VEGF.

Measurements of serum level of VEGF

Blood samples were collected and allowed to clot at room temperature for about 1 h. The samples were then centrifuged at 3000×g for 10 min, and the sera collected. The serum samples were stored in aliquots at −80°C until analyses. ELISAs were used to determine the serum level of VEGF (Quantikine HS, R&D Systems, Minneapolis, Minnesota, USA).

Optical coherence tomography

The pRT was measured with the RS3000 advance spectral domain OCT (SD-OCT; NIDEK, Gamagori, Japan). A circular scan centred on the optic disc (3.45 mm diameter, 'Disc Circle' mode, software NAVIS-EX V.1.5.0) was recorded through a dilated pupil. The scan consisted of 1024-A scan with high-definition (50 HD) frame enhancement software that measured the pRT along a circle of 3.45 mm diameter around the optic disc. The pRT was measured automatically as the distance between the ILM and the outer border of the RPE with the software in the RS3000 SD-OCT (figure 2A, B). The average pRT was used for the statistical analyses. All images were acquired by a single well-trained operator (MK) who was masked to the diagnosis of POEMS syndrome and other clinical findings.

Intracranial pressure

After the ophthalmic examinations, LP was performed in all patients using a standard 18-guage or 20-gauge spinal needle and a manometer positioned at a 90-degree angle to the spine. The opening LP pressure was measured while the subject was placed in lateral decubitus position with legs extended, head and spine strictly horizontal, and as relaxed as possible. Sufficient time was allowed for the pressure to stabilise. The pRT and the opening LP pressure were measured within 2 week after the blood samples were collected. The opening LP pressure was defined as the ICP.

Statistical analyses

Statistical analysis was performed using SPSS software for Microsoft Windows (SPSS V.20, IBM Japan, Tokyo). The correlations between the pRT and the serum level of VEGF in POEMS patients were determined by the Spearman's rank-correlation coefficient. The correlation between the pRT of the right and left eyes in POEMS patients was determined by the

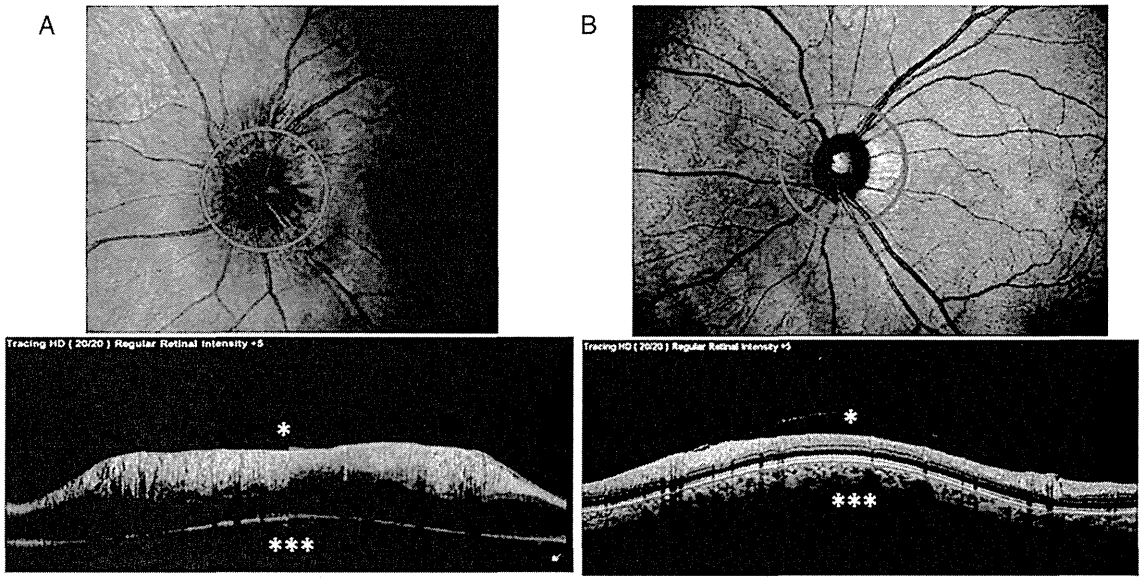

Figure 2 Peripapillary retinal thickness (pRT) analysis. Optical coherence tomographic (OCT) images of patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome with papillary oedema (A; left eye of case 16) and without papillary oedema (B; left eye of case 4). Disc Circle protocol was centred on the optic nerve head to measure the pRT around a 3.45 mm-diameter circle. Average pRT thickness measurement was used for the statistical analyses. Red line and purple line represent the OCT algorithm outlining the pRT: the anterior border (*) towards the internal limiting membrane and the posterior border (***) at the outer border of retinal pigment epithelium (RPE) line.

intraclass correlation coefficient (ICC). Mann–Whitney U tests were used to determine if the differences between groups were statistically significant. In addition, multivariable logistic regression analysis was performed to identify independent factors, for example, serum VEGF, ICP, age and IOP, which were correlated with the average pRT of the two eyes of each patient. Statistical significance was defined as $p<0.05$.

RESULTS

The demographics of the 17 Japanese patients with POEMS syndrome (9 men, 8 women) are shown in table 1.

Their mean age was 51.4±13.5 years with a range from 36 to 73 years. The mean IOP was 11.9±2.0 mm Hg with a range from 9 to 16 mm Hg. The mean pRT was 344.8±100.7 μm for the right eyes and 362.8±124.1 μm for the left eyes. The difference in the mean pRT between the right and the left eyes was not significant ($p=0.55$, Mann–Whitney U test), but there was a significant correlation between the pRT of the right and left eyes with an ICC of 0.839 (figure 3). Thirteen patients (76%) had bilateral ODO that was detected by indirect ophthalmoscopy.

The mean serum level of VEGF in all patients was 6085±3332 pg/mL with a range of 1380–12 000 pg/mL, which is almost 30-fold higher than that of normal subjects (219 pg/mL).[17] The mean opening LP pressure in all patients was 137.9±33.7 mm H_2O with a range of 100–195 mm H_2O, which is almost within normal range of 120–206 mm H_2O.[12]

There was a significant positive correlation between serum levels of VEGF and the average pRT of the two eyes of each patient ($r=0.81$, $p<0.0001$, Spearman's rank correlation; figure 4).

The difference in the serum VEGF concentrations between patients with ODO (7086±3115 pg/mL) and without ODO (2835±1408 pg/mL) was also significant ($p=0.029$, Mann–Whitney U test).

Multiple regression analysis showed that the serum level of VEGF was an independent contributor to the average pRT of the two eyes of each patient (VEGF, standard regression coefficient=0.59, $p=0.012$; ICP, standard regression coefficient=0.076, $p=0.73$; age, standard regression coefficient=0.052, $p=0.81$; IOP, standard regression coefficient=0.21, $p=0.34$).

DISCUSSION

The pathogenesis of POEMS syndrome is complex, and several systemic factors are thought to be involved. The results of

Table 1 Patient characteristics and optical coherence tomography data and serum levels of VEGF

Patient	Age	Sex	Eye	BCVA	Intraocular pressure (mm Hg)	Peripapillary retinal thickness (μm)	Intracranial pressure (mm H_2O)	Serum levels of VEGF (pg/mL)	Optic disc oedema
1	57	F	OD	1	11	301	125	6400	+
			OS	1.2	13	328			+
2	61	M	OD	1.2	11	388	110	11 600	+
			OS	1.2	11	298			+
3	69	F	OD	1.2	13	287	105	3150	+
			OS	1.2	13	294			+
4	56	M	OD	0.6	9	217	120	1960	–
			OS	0.6	10	254			–
5	73	M	OD	1.2	10	287	140	3910	+
			OS	1.2	10	311			+
6	39	M	OD	1.2	15	316	195	2230	+
			OS	1.2	14	334			+
7	63	M	OD	1.2	16	323	160	5220	+
			OS	1.2	15	291			+
8	38	F	OD	1.2	9	341	190	6420	+
			OS	1.2	9	347			+
9	36	F	OD	1.2	12	263	195	1380	–
			OS	1.2	12	250			–
10	38	M	OD	1.2	12	324	140	6110	+
			OS	1.2	11	299			+
11	57	M	OD	1.2	10	447	170	10 600	+
			OS	1.2	9	553			+
12	38	M	OD	1.2	12	266	140	4420	–
			OS	1.2	11	266			–
13	34	F	OD	1.2	10	328	105	12 000	+
			OS	1.2	11	327			+
14	49	F	OD	1.2	14	291	100	3580	–
			OS	1.2	15	287			–
15	65	F	OD	0.7	14	361	120	7250	+
			OS	1.2	14	503			+
16	64	F	OD	1.2	15	479	90	8170	+
			OS	1.2	10	635			+
17	36	M	OD	1.2	13	643	140	9060	+
			OS	1.2	12	592			+

BCVA, best-corrected visual acuity; OD, right eye; OS, left eye; VEGF, vascular endothelial growth factor.

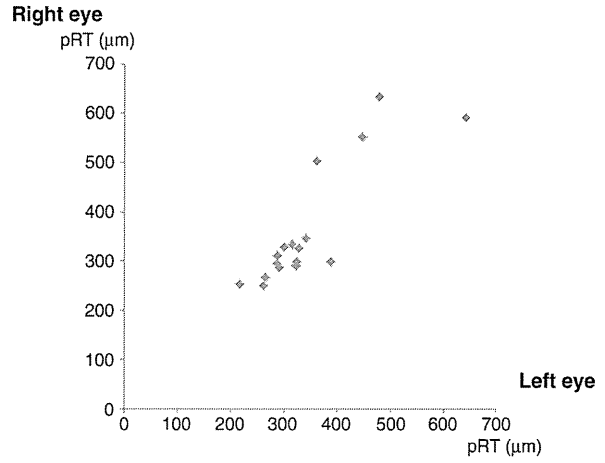

Figure 3 Correlation between the peripapillary retinal thickness (pRT) of right and left eyes in patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome. There was a significant correlation between the pRT of right and left eyes in patients with POEMS syndrome with an intraclass correlation coefficient of 0.839.

several studies suggested that a hyperproduction of VEGF by abnormal plasma cells was the major contributor to the development of POEMS syndrome.[9] The elevated levels of VEGF may also account for the ODO as it has been suggested that ODO is due to higher levels of VEGF.

ODO was detected bilaterally in 13 patients (76%), which is consistent with earlier reports that bilateral ODO was the most common (30%–70%) sign in POEMS syndrome.[1 4 6 8 11] The cause of the ODO in POEMS syndrome has not been determined, but it has been suggested that an elevated ICP,[7–9 11] vasculitis,[18] presence of cerebrospinal fluid proteins,[11] infiltrations into the optic nerve,[19] or increased VEGF levels[4 8 10 20] may be involved.

It has also been reported that the increased vascular permeability associated with elevated VEGF serum levels may contribute to the development of ODO.[4 8 10 20] This concept of

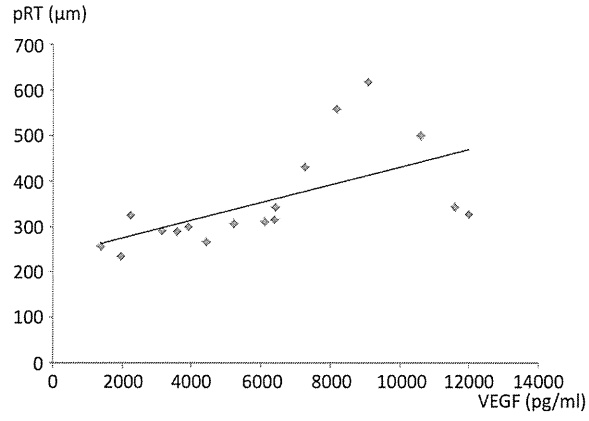

Figure 4 Correlation between serum levels of vascular endothelial growth factor (VEGF) and the average peripapillary retinal thickness (pRT) of two eyes of each patient with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome. There was a significant positive correlation between serum levels of VEGF and the average pRT of the two eyes of each patient ($r=0.81$, $p<0.0001$, Spearman's rank correlation).

microvascular hyperpermeability is supported by the presence of oedema elsewhere in the body of patients with POEMS syndrome.[4]

Okada reported that the ODO in POEMS syndrome was correlated with the serum level of VEGF as we found, and patients with ODO responded well to systemic autologous peripheral blood stem cell transplantation.[20] Kaushik also suggested a possible association between plasma VEGF and ODO because the median plasma VEGF level at the initial presentation was 300 pg/mL, which was significantly higher than the median VEGF level after the ODO resolved (51 pg/mL).[8]

However, these earlier reports were small case series or single case reports, and to the best of our knowledge, our study is the first to investigate the relationship between the serums levels of VEGF and the pRT by SD-OCT in a large number of patients with POEMS syndrome. The reason why the pRT was used in this study was that some patients had bilateral high grade of papilloedema with a Modified Frisen Scale of grade 4 or 5. Colin *et al* reported that the failure rates of retinal nerve fibre layer (RNFL) thickness measurements increased as the degree of disc oedema increased, and that the algorithm defining total retinal thickness had a lower failure rate than that defining the RNFL thickness.[14] Therefore, Colin *et al* reported that for lower grade papilloedemas, the RNFL thickness measurement was useful, but with higher-grade papilloedemas, the total retinal thickness was obtained more accurately,[14] and that the OCT total retinal thickness measurements might be more useful especially for higher grades of papilloedemas.[14]

The significantly higher levels of serum VEGF in patients with than without ODO and the significant positive correlation between the pRT and the serum levels of VEGF suggest that the elevated serum VEGF was the cause of the ODO in patients with POEMS syndrome as reported.

However, some earlier case reports, a small series study[7–9 21] and a clinical study[11] suggested that the presence of intracranial hypertension may be a contributing factor to the ODO in POEMS syndrome, although some small series have found no relationship between ODO and raised ICP.[5 6 18 22 23] These results suggest that an elevated ICP may be a mechanical explanation for the development of ODO in POEMS syndrome because the ICP can be transmitted to the optic disc causing ODO.[8]

Kaushik reported that patients with ODO had a higher mean opening LP (276 mm H_2O, three patients) than patients without ODO (176 mm H_2O, two patients), although the difference was not statistically significant ($p=0.08$).[8] Wiaux also reported that two patients had elevated ICP of 300 and 390 cm H_2O.[7]

In our patients, the mean opening LP pressure in all patients was almost within the normal range of ICP,[12] and was lower than these case reports.[7 8] In addition, the difference in the mean opening LP pressure between patients with ODO (132 mm H_2O, 13 patients) and patients without ODO (120 mm H_2O, four patients) was not significant ($p>0.05$, Mann–Whitney U test).

In addition, the correlation between the pRT and the opening LP pressure was not significant in our patients ($p>0.05$, Spearman's rank-correlation coefficient; data not shown). The multiple regression analysis showed that the ICP was not an independent contributor to the pRT in our patients (standard regression coefficient=0.076, $p=0.73$). Thus, we believe that the effect of ICP had a minimal effect on the ODO in our patients.

There was a significant correlation between the serum levels of VEGF and the average pRT of the two eyes of each patient

(r=0.81, p<0.0001, figure 4). However, the pRT peaked at about 9000 pg/mL and then decreased (figure 4). The reason why the pRT peaked at about 9000 pg/mL and then fell is that Case 2 (11 600 pg/mL) and Case 13 (12 000 pg/mL) had myopia with axial lengths of 26.04 and 26.1 mm, respectively and their retinas appeared to be thin. To exclude the effect of high myopia, all of our patients whose axial length was >26.5 mm were excluded, but we believe that it may not have been completely excluded in these eyes.

Our study has several limitations. First, the possible effects of factors other than the ICP and level of VEGF on the ODO must be taken into consideration. Other factors hypothesised to contribute to ODO, such as infiltration by abnormal proteinaceous material,[19] were not examined, although we could find no lesions suggesting infiltrations into the choroid, orbit, or optic nerve in our cases. In addition, we did not find any systemic abnormalities such as differences in the body mass index. Second, our results cannot answer the question of a cause–effect relationship between ODO and raised VEGF. Further studies are needed to determine whether treatment of POEMS syndrome, such as high-dose chemotherapy with autologous peripheral blood stem-cell transplantation, anti-VEGF monoclonal antibody (bevacizumab) therapy and thalidomide therapy, can lead to a decrease in the pRT thickness by reducing the serum VEGF level. Finally, we were not able to determine whether ODO is more likely related to VEGF concentration, and further studies with a larger sample size may help to explain this and also explain the mechanism of ODO in patients with POEMS syndrome.

In conclusion, we found a significant correlation between the pRT and serum level of VEGF in patients with POEMS syndrome and we also found the significantly higher serum VEGF concentrations in patients with POEMS syndrome and ODO. In addition, the multiple regression analysis showed that the serum level of VEGF was an independent contributor to the pRT. These results suggest that raised VEGF might explain the development and mechanism of ODO in patients with POEMS syndrome. In addition, our findings indicate that OCT can be helpful in the ophthalmic evaluations of patients with POEMS syndrome.

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Contributors Design and conduct of study: HY, TB and SS. Collection, management, analysis and interpretation of the data: HY, TB, MK, TO and SM. Preparation, review or approval of the manuscript: HY, TB, SY and SK.

Competing interests None declared.

Patient consent Obtained.

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