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RETINAL DISORDERS

Correlation between serum level of vascular endothelial growth factor and subfoveal choroidal thickness in patients with POEMS syndrome

Hirotaka Yokouchi · Takayuki Baba · Sonoko Misawa · Setsu Sawai · Minako Beppu · Masayasu Kitahashi · Toshiyuki Oshitari · Satoshi Kuwabara · Shuichi Yamamoto

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Abstract
Purpose The study was conducted to determine whether serum vascular endothelial growth factor (VEGF) levels are significantly correlated with subfoveal choroidal thickness (CT) and foveal thickness (FT) in patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome.
Patients and methods In this cross-sectional observational case series, we studied 31 eyes of 16 treatment-naïve patients with POEMS syndrome with no evidence of fundus abnormalities. Subfoveal CT and FT were measured using enhanced depth imaging optical coherence tomography (EDI-OCT), and correlations between serum VEGF levels and subfoveal CT and FT were determined.
Results The mean subfoveal CT was 417.9±73.5 μm (right eye, 416.7±81.2 μm; left eye, 419.0±68.1 μm), and the mean FT was 243.8±35.2 μm (right eye, 248.8±22.0 μm; left eye, 239.1±44.6 μm). There was a significant positive correlation between the serum VEGF level and subfoveal CT (right eye, r=0.58, p=0.021; left eye, r=0.60, p=0.012), but the correlation between the level of serum VEGF and FT was not significant (right eye, r=0.007, p>0.05; left eye, r=0.25, p> 0.05).
Conclusions The significant correlation between the serum VEGF level and subfoveal CT in patients with POEMS syndrome suggests that choroidal thickness is influenced by the level of serum VEGF. These results not only aid in an understanding of the pathogenesis of ocular changes in patients with POEMS syndrome, but also offer clues regarding the pathogenesis of other choroidal diseases.

Keywords POEMS syndrome · Vascular endothelial growth factor (VEGF) · Subfoveal choroidal thickness · Foveal thickness

Introduction

The term "POEMS" syndrome refers to a multi-system disorder that is characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes, and which is associated with plasma cell dyscrasia [1, 2]. Although the pathogenesis of the disease has not been definitively determined, it has been suggested that overproduction of vascular endothelial growth factor (VEGF) plays an important role. VEGF strongly promotes neovascularization and enhances vascular permeability [3–5], and these changes are responsible for the characteristic signs of POEMS syndrome, including angiomata, pleural effusion/ascites, edema, and organomegaly [3]. It is thought that VEGF is inappropriately secreted by monoclonal plasma cells [4, 5]; if this can be proven, these cells could be targeted for the treatment of POEMS syndrome [5].

H. Yokouchi (✉) · T. Baba · M. Kitahashi · T. Oshitari · S. Yamamoto
Departments of Ophthalmology and Visual Science, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, chuo-ku, Chiba City, Chiba 260-0856, Japan
e-mail: yokouchi123@peace.ocn.ne.jp

S. Misawa · S. Sawai · M. Beppu · S. Kuwabara
Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan

S. Sawai
Molecular Diagnosis, Graduate School of Medicine, Chiba University, Chiba, Japan

S. Sawai
Division of Laboratory Medicine and Clinical Genetics, Chiba University Hospital, Chiba, Japan

Data on the incidence and the spectrum of ocular abnormalities associated with POEMS syndrome are limited, and the pathogenesis of the disease has not been determined. The major ocular finding in POEMS syndrome is optic disc edema [5–7]. Examination of the eyes of patients with POEMS syndrome using spectral-domain optical coherence tomography (SD-OCT) has shown serous retinal detachment (SRD) [8] and cystoid macular edema (CME) [6]. Conventional SD-OCT cannot provide clear imaging of the entire choroid, but such images can be obtained using enhanced depth imaging (EDI)-OCT, and these images can be used to measure the thickness of the choroid [9]. As such, EDI-OCT has been used to measure choroidal thickness in normal eyes [10, 11], in eyes with central serous chorioretinopathy (CSC) [12] and Vogt–Koyanagi–Harada (VKH) disease [13], in highly myopic eyes [14], and in eyes with retinitis pigmentosa (RP) [15]. However, EDI-OCT has not been used to study the choroid in eyes with POEMS syndrome.

The purpose of this study, therefore, was to determine the subfoveal choroidal and foveal thickness in the eyes of patients with POEMS syndrome, and also to determine whether there was a significant correlation between subfoveal choroidal thickness and serum VEGF levels.

Methods

We reviewed the medical records of 31 eyes of 16 treatment-naïve patients with POEMS syndrome at the Chiba University Hospital from November 2011 through September 2013. The diagnosis of POEMS syndrome was made using criteria established by Dispenzieri in 2007 [5].

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

Patients were excluded if even one eye had any of the following: (1) axial length greater than 26.5 mm, (2) refractive error (spherical equivalent)>−6.0 diopters (D); (3) intraocular pressure >21 mmHg; (4) history of intraocular surgery, history of retinal or choroidal vascular disease, or glaucoma.

Serum samples were obtained from all of the patients, and data was collected, including best-corrected visual acuity (BCVA) using Snellen charts, intraocular pressure, refractive errors, axial length, and slit-lamp and fundus findings.

The major outcomes were subfoveal choroidal thickness (CT), foveal thickness (FT), and VEGF serum levels. The changes in the subfoveal CT and FT were determined using SD-OCT (Heidelberg Spectralis OCT; Heidelberg, Germany) images (Fig. 1). Each image was obtained using the eye tracking system, and 100 scans were averaged to increase the signal-to-noise ratio [9] using an EDI-OCT algorithm. The subfoveal CT was measured from the outer border of RPE to the inner border of sclera using software in the Heidelberg Spectralis OCT. The subfoveal CT and FT were measured vertically in a horizontally scanned image through the center of the fovea. Measurements of OCT images were made by two of the authors (MK, TO), who were masked to VEGF serum levels. The average of the two measurements was used. Differences between the readings of the two observers were found to be within 10 % of the mean.

Measurement of VEGF serum levels

After the blood samples were collected, they were allowed to clot at room temperature for about one hour, and were then centrifuged at 3,000×g for 10 minutes. Serum samples were stored in aliquots at −80 ° C until analyses were performed. Enzyme-linked immunosorbent assays (ELISAs) were used to determine serum VEGF levels (Quantikine HS®, R&D Systems, Minneapolis, MN, USA). The subfoveal CT and FT were measured within one week after collection of blood samples.

Statistical analyses

The correlations between the serum VEGF levels and subfoveal CT and FT in POEMS patients were determined

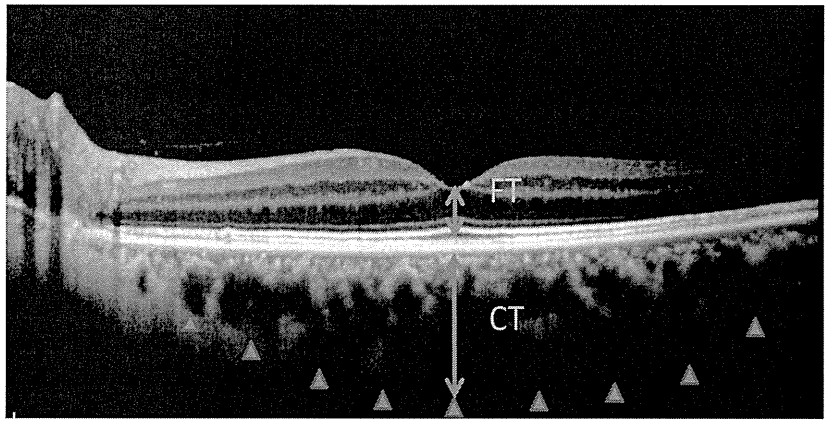

Fig. 1 Enhanced depth images of a patient with POEMS syndrome (Case 12, left eye) with choroidal thickening. CT choroidal thickness, FT foveal thickness

using Spearman's rank correlation coefficient. Statistical significance was defined as $p < 0.05$.

Results

Sixteen Japanese patients with POEMS syndrome (12 men, 4 women) were studied. The demographics of the patients are shown in Table 1.

The mean age of patients was 56.3±11.4 years, with a range from 36 to 75 years, and the mean intraocular pressure was 12.3±2.8 mmHg, with a range from 9 to 20 mmHg. Eleven patients (68.7 %) had optic disc edema detected by indirect ophthalmoscopy, and the edema was bilateral in seven patients (43.7 %) and unilateral in four patients (25 %). Cystoid macular edema (CME) and serous retinal detachment (SRD) were not detected in any of the eyes by ophthalmoscopy and SD-OCT. The mean refractive error (spherical equivalent) was −0.40±1.55 diopters (D), with a range from −4.75 to 2.75 D, and the mean axial length was 23.6±1.00 mm, with a range from 21.8 to 25.7 mm. The mean subfoveal CT was 417.9±73.5 μm for both eyes; it was 416.7±81.2 μm for the right eye and 419.0±68.1 μm for the left eye. The mean FT

Table 1 Patient characteristics, OCT data, and serum VEGF levels

Patient	Age	Sex	Eye	BCVA	AL(mm)	IOP(mmhg)	SE(D)	FT(μm)	SCT(μm)	VEGF(pg/ml)	ODE
1	54	F	OD	1	23.5	11	−0.5	280	361	3,380	+
			OS	1.2	23.2	13	−0.25	275	379		+
2	59	M	OD	1.2	25.1	12	−2	285	465	11,000	+
			OS	1.2	25.6	12	−2.25	278	432		+
3	66	F	OD	1.2	22.2	13	−0.25	206	396	5,590	−
			OS	1.2	22.2	13	−0.75	224	381		+
4	75	M	OD	1.2	23.7	11	2.75	257	399	9,690	−
			OS	1.2	23.5	12	2.75	250	408		−
5	50	M	OD	0.6	23.1	17	1.5	249	236	1,330	−
			OS	0.6	22.6	19	2.5	122	297		−
6	56	M	OD	1	21.8	9	−0.5	233	387	1,760	−
			OS	1.2	21.9	10	0.5	235	419		+
7	66	M	OS	0.6	21.9	10	−1	156	409	1,350	−
8	72	M	OD	1	23.2	11	−1	270	350	2,460	−
			OS	1	23.4	11	−1	285	367		+
9	47	F	OD	1.2	23.7	12	−0.25	218	465	4,590	−
			OS	1.2	23.7	13	0	238	389		−
10	62	M	OD	1.2	24.3	11	−1	252	463	8,430	+
			OS	1.2	23.9	12	−0.75	282	448		+
11	36	M	OD	1.2	23.6	10	−1	253	495	7,600	+
			OS	0.2	23.5	13	−0.5	247	528		−
12	61	M	OD	0.8	24	20	0	249	581	8,970	−
			OS	1.2	23.9	16	−1	271	467		−
13	55	M	OD	1.2	22.9	10	−0.25	240	416	11,200	+
			OS	1.2	22.9	9	−0.25	239	484		+
14	45	M	OD	1.2	25.7	11	−4.75	266	332	5,360	+
			OS	1.2	25.3	13	−3.5	265	318		+
15	61	M	OD	1.2	23.9	16	0.75	225	430	11,900	+
			OS	1.2	23.8	15	0.75	220	425		+
16	36	F	OD	1.2	24.2	9	−0.5	249	475	6,420	+
			OS		24.1	9	−0.75	240	554		+
Mean	56.3				23.6	12.3	−0.4	243.8	417.9	6,314	
SD	11.4				1	2.8	1.55	35.2	73.5	3,648	

BCVA best-corrected visual acuity, *AL* axial length, *IOP* intraocular pressure, *SE* spherical equivalent, *FT* foveal thickness, *SCT* subfoveal choroidal thickness, *OCT* optical coherence tomography, *VEGF* vascular endothelial growth factor, *ODE* optic disc edema

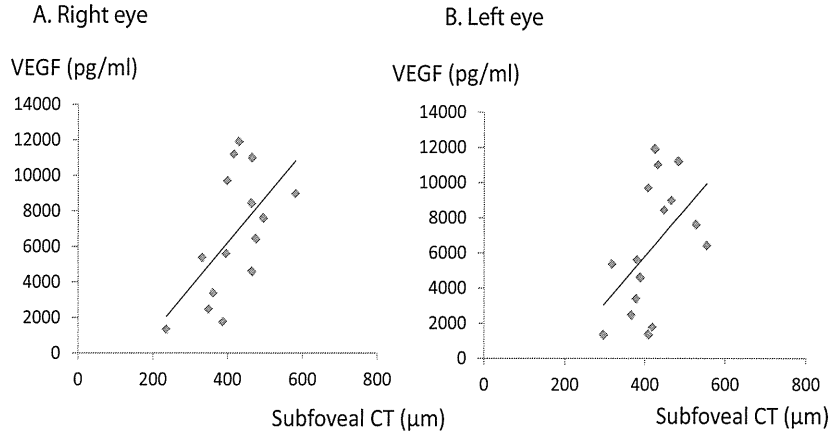

Fig. 2 Correlation between subfoveal choroidal thickness (CT) of both eyes and serum VEGF levels in patients with POEMS syndrome. There was a significant correlation between subfoveal CT and serum VEGF in patients with POEMS syndrome. (**a**) right eye, r=0.58, p=0.021, (**b**) left eye, r=0.60, p=0.012, Spearman's rank correlation coefficient

was 243.8±35.2 μm for both eyes; it was 248.8±22.0 μm in the right eyes and 239.1±44.6 μm in the left eyes. The mean serum VEGF level among patients was 6,314±3,648 pg/ml, with a range of 1,330 to 11,900 pg/ml, which is almost 30-fold higher than that of normal subjects (219 pg/ml) [16].

There was a significant positive correlation between the serum VEGF level and subfoveal CT (right eye, r=0.58, p=0.021; left eye, r=0.60, p=0.012; Fig. 2). In addition, there was a strong positive correlation between the subfoveal CT of right eyes and left eyes (r=0.77, P=0.00034). On the other hand, the correlation between the serum VEGF levels and FT was not significant for the right eyes (r=0.007, p >0.05) or left eyes (r=0.25, p>0.05; Fig. 3.).

Discussion

The pathogenesis of POEMS syndrome is complex, and several systemic factors are thought to be involved. The results of several studies have suggested that hyperproduction of VEGF by abnormal plasma cells is the major contributor to the development of POEMS syndrome [1, 2]. We found bilateral optic disc edema in seven patients (43.7 %), which is consistent with reports that bilateral optic disc edema was the most common (30–70 %) sign associated with POEMS syndrome [5–7].

The difference in serum VEGF concentrations between patients with and without optic disc edema was not significant (p=0.35). It has been reported that both elevated intracranial pressure (ICP) [2, 17] and elevated VEGF concentration [6] are causes of optic disc edema in patients with POEMS syndrome. The difference in serum VEGF concentration between patients with and without optic disc edema was not considered significant, as elevated ICP may have affected optic disc edema in our patients.

Subfoveal CT in normal eyes, as determined by EDI-OCT, has been reported from 254 to 354 μm [9–11, 18–20]. Studies have also shown that age [10, 14], intraocular pressure [21, 22], refractive error [14], and axial length [21, 22] can affect CT. In addition, the choroid in highly myopic eyes is very thin and undergoes further thinning with increasing age and degree of myopia [14]. An increase in the IOP is associated with choroidal thinning and elongation of the axial length [21]. The mean age of our patients was 56.3±11.4 years (range from 36 to 75 years), the mean intraocular pressure was 12.3± 2.82 mmHg (range, 9 to 20 mmHg), and the mean axial length was 23.6±1.0 mm (range, 21.8 to 25.7 mm). The correlation between age and the subfoveal CT was not significant (r= 0.20, p=0.26). There was also no significant correlation

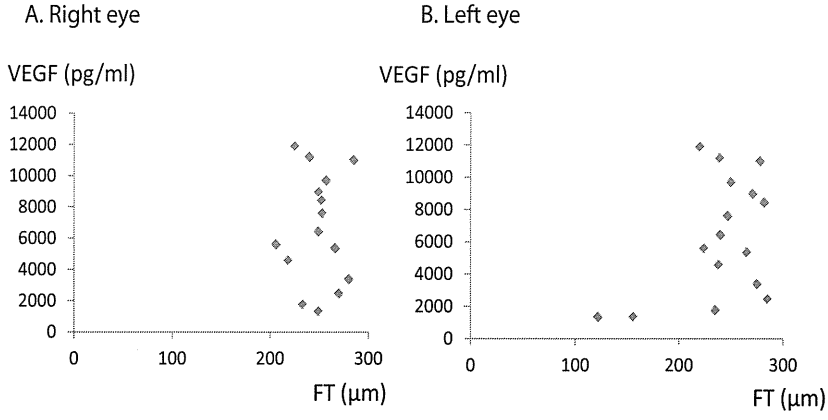

Fig. 3 Correlation between foveal thickness (FT) of both eyes and serum VEGF levels in patients with POEMS syndrome. The correlation between the FT and serum VEGF in patients with POEMS syndrome was not significant. (**a**) right eye, r= 0.007, p>0.05, (**b**) left eye, r= 0.25, p>0.05, Spearman's rank correlation coefficient

between intraocular pressure and subfoveal CT (r=0.14, P= 0.44). Likewise, the correlation between axial length and the subfoveal CT was not significant (r=0.15, p=0.40). Thus, the effects of age, intraocular pressure, and axial length were most likely minimal in our cases, and the mean subfoveal CT (417.9±73.5 μm) was thicker than that reported among studies for normal eyes (254 to 354 μm) [9–11, 18–20].

The increased choroidal thickness may be due to increased choroidal vascular permeability caused by the higher levels of VEGF. VEGF is a cytokine that targets endothelial cells, inducing neovascularization and enhancing vascular permeability [23, 24]. An increase in microvascular permeability is supported by the presence of edema elsewhere in the body—e.g., lower extremities, abdomen, pleura, and pericardium—in patients with POEMS syndrome [25]. In this study, edema was present elsewhere—e.g., lower extremities, abdomen, pleura, and pericardium—in most patients.

Alterations in the function and structure of the choroid are known to play a role in the pathogenesis of several ocular disorders. Recent studies have shown that eyes with central serous chorioretinopathy (CSC) [12] and Harada disease [13] have greater subfoveal choroidal thickness. The thickened choroid in CSC may be due to increased vascular permeability, and in Harada disease it may be due to inflammation of the choroid.

Cystoid macular edema (CME) and serous retinal detachment (SRD) have been reported in eyes of patients with POEMS syndrome [8, 26]. Imai et al. [26] suggested that CME in these cases was due to elevated serum VEGF and not to the VEGF secreted from retinal tissues. It has been reported that patients with POEMS syndrome can develop SRD or macular edema (ME) during the course of the disease process [6, 8, 26]. In our cases, the foveal thickness of the left eyes in Cases 5 and 7 were very thin, although we could not find a history of retinal and choroidal diseases. Because these patients had a longer duration of POEMS syndrome, the optic disc edema, SRD, and ME might have developed unknowingly during the course of the disease. Thus, we believe that these disease processes may have caused the reduction in retinal thickness, although we did not detect signs of these diseases in either case during the study. In Case 7, the right eye was phthisic due to trauma that occurred in childhood. Thus, data of the right eye in Case 7 are not known.

In contrast, the correlation between the serum levels of VEGF and FT was not significant. It is well known that VEGF is a cytokine that can affect vascular permeability via intravascular compartments [23, 24]. The reason why such high serum VEGF did not cause retinal edema is that the increased levels of serum VEGF in the choroidal vasculature may be due to the larger caliber and greater volume of flow in comparison with the retinal circulation. Thus, high serum VEGF may not cause retinal edema, and the serum levels of VEGF may have a greater effect on choroidal than on retinal tissues.

Our study had several limitations. First, the possible effects of other factors such as systemic or topical medications, diurnal variations, and nutrition on choroidal thickness must be taken into consideration. Second, our results cannot answer the question of a cause–effect relationship between increased serum levels of VEGF and increased choroidal thickness. Further studies are needed to determine whether treatment of POEMS syndrome such as high-dose chemotherapy with autologous peripheral blood stem-cell transplantation (auto-PBSCT), anti-VEGF monoclonal antibody (bevacizumab) therapy, and thalidomide therapy can lead to a decrease in choroidal thickness due to a reduction in serum VEGF level. Positive results would support the idea that the higher levels of serum VEGF were the cause of the thickened choroid in patients with POEMS syndrome. Finally, we are not able to conclude that serum levels of VEGF influence choroidal thickness in normal eyes. Further studies with a large sample size may help to explain the role of serum VEGF in the choroid of normal eyes.

In conclusion, we showed that a significant correlation between serum level of VEGF and subfoveal CT was present in patients with POEMS syndrome. These results not only aid in understanding the pathogenesis of ocular changes in patients with POEMS syndrome, but also offer clues on the pathogenesis of other choroidal diseases.

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Conflict of interest No conflicting relationship exists for any author.

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Altered axonal excitability properties and nerve edema in POEMS sydnrome

Mitsuma S, Misawa S, Shibuya K, Isose S, Sekiguchi Y, Iwai Y, Beppu M, Watanabe K, Amino H, Kuwabara S

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Altered axonal excitability properties and nerve edema in POEMS syndrome

Satsuki Mitsuma, Sonoko Misawa, Kazumoto Shibuya, Sagiri Isose, Yukari Sekiguchi, Yuta Iwai, Minako Beppu, Keisuke Watanabe, Hiroshi Amino, Satoshi Kuwabara *

Department of Neurology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan

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HIGHLIGHTS

- Axonal excitability and its correlation with serum VEGF and nerve edema detected by ultrasound were studied in POEMS syndrome.
- Excitability testing suggested possibly altered sodium, potassium, and inward rectifying currents, some of which were correlated with VEGF levels and nerve edema.
- In addition to structural changes (demyelination), nerve edema induced by upregulated VEGF, and upregulated inflammatory cytokines can modulate profiles of POEMS neuropathy.

ABSTRACT

Objective: POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare cause of demyelinating neuropathy with upregulation of vascular endothelial growth factor (VEGF). This study aimed to elucidate axonal excitability properties and their relation to VEGF levels and nerve edema in POEMS neuropathy.
Methods: Axonal excitability measurement and nerve ultrasound were performed in the median nerve of 33 patients with POEMS syndrome. Serum VEGF levels were measured by ELISA.
Results: Compared with normal subjects ($n = 87$), POEMS patients showed longer strength-duration time constant, fanning-out of threshold electrotonus curves, and greater threshold changes in a hyperpolarizing current–threshold relationship. Nerve ultrasound showed significant enlargement in POEMS patients. Serum VEGF levels and the extent of nerve edema partly correlated with nerve conduction slowing, as well as persistent sodium currents and inward rectification.
Conclusions: In POEMS syndrome, patterns of changes in excitability properties could suggest increased persistent sodium currents, and impaired potassium and inward rectifying channels. The findings were not consistent with depolarization due to nerve edema and compression ischemia.
Significance: In addition to demyelination, nerve edema induced by upregulated VEGF, and upregulated inflammatory cytokines could modulate profiles of POEMS neuropathy.

1. Introduction

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare cause of demyelinating polyneuropathy associated with monoclonal plasma cell proliferation and multi-organ involvement (Bardwick et al., 1980; Kuwabara et al., 2008a; Dispenzieri, 2014). Serum levels of vascular endothelial growth factor (VEGF) are markedly increased in POEMS syndrome, and increased vascular permeability and neovascularization mediated by VEGF are likely to cause characteristic symptoms such as edema, pleural effusion/ascites, organomegaly and skin angiomata (Watanabe et al., 1996). However, mechanisms for neuropathy in POEMS syndrome have not yet been elucidated,

* Corresponding author. Tel.: +81 43 222 7171x5414; fax: +81 43 226 2160.
E-mail address: kuwabara-s@faculty.chiba-u.jp (S. Kuwabara).

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whereas pathological studies have shown perineurial edema, and segmental demyelination with uncompacted myelin and secondary axonal degeneration (Kanda, 2013).

The proposed mechanisms for POEMS neuropathy include that the combination of blood-nerve barrier breakdown by VEGF and following invasion of other inflammatory cytokines such as interleukin-12, and tumor necrosis-α causes nerve demyelination (Kanai et al., 2012), and that nerve edema mediated by VEGF leads to compression ischemia and axonal depolarization (Kanda, 2013), but these hypotheses still need confirmation.

Axonal excitability testing using threshold tracking was developed to investigate ion channel function, membrane potential, and passive membrane properties of human axons *in vivo* (Bostock et al., 1998; Burke et al., 2001), and over the past two decades, the technique has been extensively applied to the study of the biophysical properties of human peripheral nerves and have provided important insights into axonal ion channel function in health and disease (Nodera and Kaji, 2006; Sawai et al., 2008).

Separately, nerve ultrasound is also becoming increasingly important in the diagnosis and evaluation of peripheral neuropathies particularly in the 2000's (Padua et al., 2012) providing new insights into macroscopic nerve morphology. In this study, we aimed to elucidate axonal excitability properties and their relation to nerve morphology and serum VEGF levels in patients with POEMS syndrome.

2. Methods

2.1. Subjects

This study prospectively enrolled 33 consecutive patients (25 men; age range 36–75 years, mean 55 years) with newly diagnosed POEMS syndrome, who fulfilled published criteria (Kuwabara et al., 2008a) seen at a single tertiary hospital (Chiba University Hospital) in Japan from January 2012 to September 2014. We excluded patients with renal failure because serum K^+ levels can significantly alter membrane potential and axonal excitability properties (Kiernan et al., 2000).

Normal control data for axonal excitability testing were obtained from 87 age-matched healthy subjects (49 men; age range 38–76 years, mean 56 years). Serum VEGF levels were measured by ELISA commercially (Special Reference Laboratory Co. Ltd., Tokyo, Japan). All the patients and normal control subjects gave informed consent to the study procedures, which was approved by the Ethics Committee of Chiba University Graduate School of Medicine.

2.2. Neurophysiological assessment

Neurophysiological evaluation was performed before thalidomide treatment, and in 9 patients, follow-up studies were done 3 months later. Nerve conduction studies were conducted using conventional procedures and a standard electromyography machine (Viking 4, Nicolet Biomedical Japan, Tokyo, Japan). Nerve excitability testing was performed on the median nerve at the wrist (3 cm proximal to the wrist crease) using a computerized program (QTRAC® with multiple excitability protocol, TRONDNF, Institute of Neurology, London, UK) as described previously (Kiernan et al., 2000; Nasu et al., 2014). Compound muscle action potentials (CMAPs) were recorded from the abductor pollicis brevis. Skin temperature was measured near the stimulating site and maintained above 32.0 °C (using extra heating, if necessary). Excitability indices included strength-duration time constant, threshold electrotonus, and refractoriness, supernormality, and late subnormality of the recovery cycle of axonal excitability with a single supramaximal conditioning stimulus, and a current–threshold relationship.

2.3. Nerve ultrasound

Ultrasound examination was performed with Logiq E9 (GE Healthcare Japan, Tokyo, Japan) with a 6–12 MHz electronic linear array probe at the wrist, forearm, and elbow portion of the median nerve trunk. Cross-sectional area were measured at the inner border of the thin hyperechoic epineural rim by the continuous tracing technique and the average values were calculated after serially measuring three times (Kerasnoudis et al., 2014). No additional force was applied other than the weight of the transducer and the extremities were kept in the neutral position to avoid causing any artificial nerve deformity.

2.4. Statistical analysis

All statistical tests were two-sided. The comparison of paired parameters of nerve conduction studies or excitability testing between baseline and the second examination was evaluated via the paired *t*-test with Bonferroni's correction for multiple testing. Regression analysis was performed by Pearson's correlation coefficient test. All statistical analyses were performed using JMP software, version 5.1.1 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Nerve excitability testing and ultrasound

Table 1 shows results of nerve conduction studies, and excitability testing. Nerve conduction velocities were significantly slowed consistent with primary demyelinating neuropathy. In excitability testing, strength-duration time constant was significantly longer and current required for produce 50% of the maximal CMAP was greater for POEMS patients than for normal controls. In the recovery cycle of axonal excitability, POEMS patients had greater superexcitability and smaller late subexcitability. POEMS patients showed fanning-out in threshold electrotonus particularly in the hyperpolarizing direction, and greater threshold changes to hyperpolarizing currents in current–threshold relationships (Fig. 1).

Nerve ultrasonography showed significantly greater cross-sectional area at the wrist, forearm, and elbow portion of the median nerve in patients with POEMS syndrome than in normal subjects.

3.2. Correlation with serum VEGF levels and nerve enlargement

Before treatment, serum VEGF levels were greatly increased in all patients with POEMS syndrome; the mean value was 5143 pg/ml (normal < 1000 pg/ml), ranging from 1080 to 16,400 pg/ml. Table 2 shows correlation of electrophysiological indices with serum VEGF levels and cross-sectional area at the elbow. Higher serum VEGF levels were associated with longer distal motor latency, and smaller CMAP amplitude in nerve conduction studies, and greater threshold changes to long hyperpolarizing conditioning currents.

Separately larger cross-sectional area on nerve ultrasound was associated with slower nerve conduction velocity, smaller CMAP amplitude, and loner strength-duration time constant. Serum VEGF levels and nerve cross-sectional area at the time of examination did not show significant correlation.

Table 1
Results of nerve conduction studies, axonal excitability, and ultrasound.

	Normal (n = 85)	POEMS syndrome (n = 31)	P-value
Nerve conduction study			
Distal latency (ms)	3.6 (0.4)	5.3 (1.0)	<0.0001
CMAP amplitude (mV)	10.8 (1.2)	5.7 (1.0)	<0.0001
Conduction velocity (m/s)	57.7 (6.3)	34.2 (6.1)	<0.0001
Nerve excitability testing	(n = 87)	(n = 33)	
Strength-duration property			
Strength-duration time constant (ms)	0.42 (0.008)	0.50 (0.02)	0.0002
Current for 50% CMAP (mA)	4.5 (0.2)	9.6 (0.8)	<0.0001
Recovery cycle			
Refractoriness (2.0 ms) (%)	47.9 (4.5)	38.5 (4.5)	0.06
Superexcitability (6.3 ms) (%)	−20.6 (1.3)	−26.0 (1.3)	0.04
Late subnormality (42 ms) (%)	18.5 (1.1)	9.2 (0.9)	<0.001
Threshold electrotonus			
TEd 10–20 ms (%)	69.2 (0.6)	70.7 (1.4)	0.3
TEd 90–100 ms (%)	46.1 (0.6)	48.4 (1.1)	0.07
TEh 90–100 ms (%)	−124.4 (2.4)	−136.9 (4.7)	0.02
Current threshold relationship			
50% depolarizing current (%)	51.9 (0.9)	56.3 (1.6)	0.02
100% hyperpolarizing current (%)	−309.6 (6.1)	−350.6 (13.9)	0.01
Hyperpolarizing I/V slope	0.42 (0.01)	0.36 (0.02)	0.01
Nerve ultrasound			
Cross sectional area	(n = 23)	(n = 19)	
Wrist (cm^2)	0.07 (0.01)	0.10 (0.02)	0.001
Forearm (cm^2)	0.06 (0.01)	0.08 (0.02)	<0.0001
Elbow (cm^2)	0.07 (0.01)	0.11 (0.03)	<0.0001

Data are given as mean (SEM).

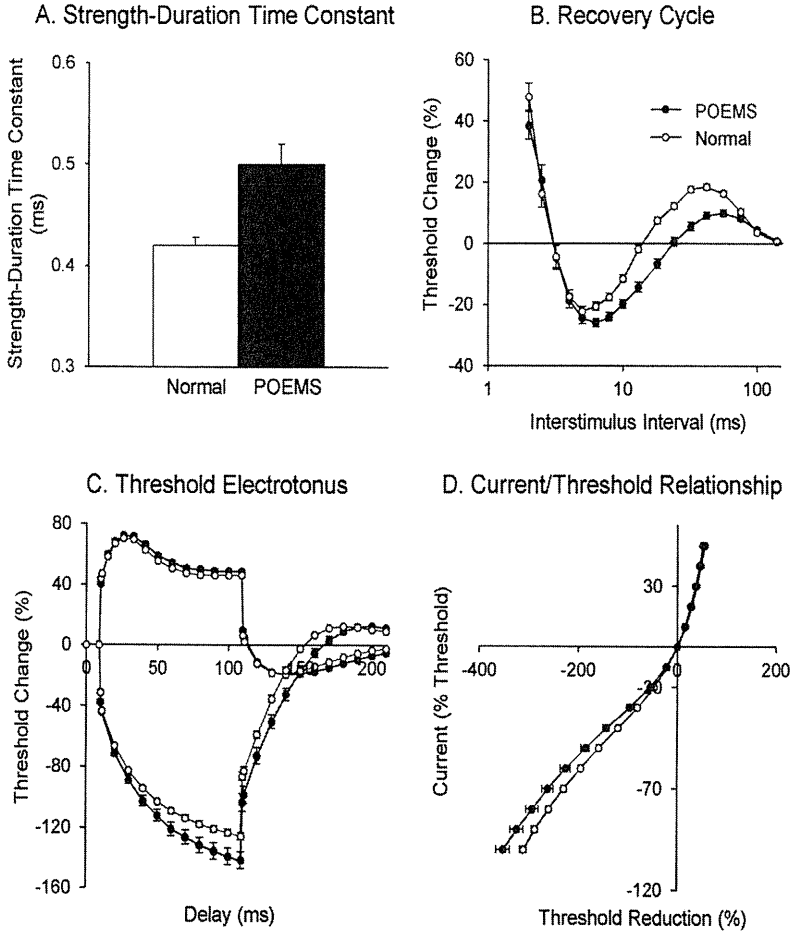

Fig. 1. Nerve excitability testing in patients with POEMS syndrome and in age-matched normal subjects. (A) Strength-duration time constant. (B) Recovery cycle of axonal excitability after supramaximal conditioning stimulus. (C) Threshold electrotonus. (D) Current–threshold relationship. Open and filled circles indicate normal subjects and POEMS patients respectively. Data are given as mean, and error bars indicate standard error.

Table 2
Correlation of electrophysiological index with VEGF and nerve edema.

	Serum VEGF level		Area (ultrasound)	
	R^2	*P*-value*	R^2	*P*-value*
Nerve conduction study				
Motor nerve conduction velocity	0.0593	NS	0.389	0.03
Distal latency	0.133	0.04	0.3344	NS
CMAP amplitude	0.2082	0.01	0.2203	0.04
Nerve excitability testing				
Stimulus (mA) for 50% max response	0.05	NS	0.1616	NS
Strength-duration time constant (ms)	0.14	NS	0.3211	0.04
Refractoriness at 2 ms (%)	0.0098	NS	0.0241	NS
Superexcitability (%)	0.015	NS	0.0042	NS
Subexcitability (%)	0.0238	NS	0.0372	NS
TEd(10–20 ms)	0.0001	NS	0.005	NS
TEd(90–100 ms)	0.0164	NS	0.01	NS
TEh(90–100 ms)	0.0185	NS	0.0125	NS
TEh(slope 101–140 ms)	0.1941	0.01	0.0241	NS
Hyperpolarizing I/V slope	0.2007	0.03	0.015	NS
Nerve ultrasound (cross-sectional area)				
Wrist	0.0218	NS		
Forearm	0.0987	NS		
Elbow	0.0208	NS		

* *P*-value <0.05, considered as statistically significant; NS, not significant.

Table 3
Serum VEGF level, electrophysiology, and nerve ultrasound before and after treatment.

	Before	3 months	*P*-value
Serum VEGF (pg/mL)	6061 (1667)	3600 (1406)	0.2
Nerve conduction study (n = 9)			
Distal latency (ms)	5.6 (0.5)	5.2 (0.5)	0.01
CMAP amplitude (mV)	5.2 (1.2)	5.1 (1.5)	0.9
Conduction velocity (m/s)	36.2 (3.6)	37.4 (3.4)	0.3
Nerve excitability testing (n = 9)			
Strength-duration time constant			
Strength-duration time constant (ms)	0.49 (0.01)	0.52 (0.04)	0.5
Current for 50% CMAP (mA)	11.3 (1.9)	8.7 (1.3)	0.2
Recovery cycle			
Refractoriness (2.5 ms) (%)	16.0 (4.2)	8.4 (6.1)	0.3
Superexcitability (7.9 ms) (%)	−27.1 (1.4)	−23.5 (1.6)	0.036
Late subnormality (42 ms) (%)	8.8 (1.2)	11.3 (1.7)	0.2
Threshold electrotonus			
TEd 10–20 ms (%)	74.4 (1.9)	74.8 (2.2)	1.0
TEd 90–100 ms (%)	51.5 (2.2)	51.5 (1.9)	1.0
TEh 90–100 ms (%)	−150.8 (10.4)	−154.0 (11.5)	0.8
Current threshold relationship (I/V)			
50% depolarizing current (%)	57.1 (2.0)	56.8 (2.0)	0.8
100% hyperpolarizing current (%)	−395.5 (19.6)	−331.8 (18.0)	0.006
Hyperpolarizing I/V slope	0.32 (0.01)	0.41 (0.04)	0.03
Nerve ultrasound (n = 13)			
Cross sectional area			
Wrist (cm^2)	0.11 (0.03)	0.10 (0.03)	0.02
Forearm (cm^2)	0.09 (0.02)	0.08 (0.02)	0.18
Elbow (cm^2)	0.12 (0.03)	0.10 (0.01)	0.01

Data are given as mean (SEM).

3.3. Serial changes after treatment

Sequential examinations on nerve excitability and ultrasound were performed before and 3 months after thalidomide treatment in 9 patients. Table 3 shows serial changes. Serum VEGF levels decreased. Nerve cross-sectional area significantly reduced after treatment, suggesting edema was a major cause of nerve enlargement. Significant improvement was observed in distal latency in nerve conduction studies. In excitability testing, superexcitability and threshold change to 100% hyperpolarizing conditioning currents in current–threshold relationship significantly changed towards normal (Fig. 2).

4. Discussion

Our results show that axonal excitability properties in POEMS neuropathy is characterized by prolonged strength-duration time constant, increased superexcitability, reduced late subexcitability, fanning-out in threshold electrotonus, and greater threshold changes to 100% hyperpolarizing conditioning current in current–threshold relationships. These findings could suggest altered nodal persistent sodium currents, reduced potassium and inward rectifying conductances, respectively (Burke et al., 2001; Nodera and Kaji, 2006; Howells et al., 2012). However, their interpretations are difficult because of multiple factors such as segmental demyelination, nerve edema, and upregulated inflammatory cytokines could contribute to altered channel function. The excitability indices and nerve conduction parameters are partly correlated with serum VEGF levels and the extent of nerve enlargement.

Pathological studies have shown segmental demyelination and remyelination, uncompacted myelin, and perineurial edema in sural nerve specimen of patients with POEMS syndrome (Koike et al., 2008). The short-internode associated with remyelination, and altered myelin resistance may affect the input resistance and lead to fanning-out in threshold electrotonus, but again other factors could modulate a total findings of excitability testing.

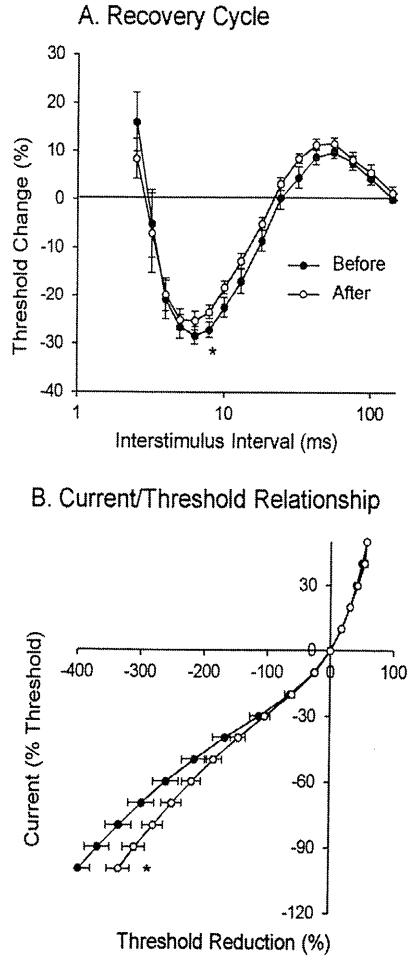

Fig. 2. Sequential changes in nerve excitability testing before and 3 months after the start of thalidomide or steroid treatment in patients with POEMS syndrome. (A) Recovery cycle of axonal excitability after supramaximal conditioning stimulus. (B) Current–threshold relationship. Filled and open circles indicate before and after treatment respectively. Data are given as mean, and error bars indicate standard error.

The pattern of excitability changes are different from those in chronic inflammatory demyelinating polyneuropathy (CIDP); previous reports on CIDP have shown that compared with normal subjects, strength-duration time constant was significantly shorter, and in the recovery cycle, CIDP patients had less refractoriness, supernormality and late subnormality than healthy controls (Cappelen-Smith et al., 2000; Sung et al., 2004). Current–threshold relationships did not show significant changes. Particularly, strength-duration time constant and superexcitability change to the opposite direction in POEMS syndrome and CIDP. It is important to differentiate the two conditions because POEMS syndrome is often misdiagnosed as CIDP (Nasu et al., 2012), but treatments are substantially different. In this regard, whether nerve excitability testing is helpful for the differential diagnosis of POEMS syndrome and CIDP, needs to be studied in a prospective fashion.

In the present study, serum VEGF levels were invariably elevated in POEMS patients, consistent with previous reports (Kuwabara et al., 2008a,b), and correlated, although weakly, with distal latency and hyperpolarizing threshold electrotonus and current–threshold relationships (Table 2). These findings might not reflect the direct effects of VEGF alone, because multiple inflammatory cytokines such as interleukin-12, and tumor necrosis-α are simultaneously and markedly upregulated in the active phase of POEMS syndrome (Kanai et al., 2012), and it is possible such cytokines other than VEGF affect ion channel function, although this should be investigated in further studies. Nevertheless, increased vascular permeability mediated by VEGF presumably responsible for nerve edema, frequently found on pathological examination (Kanda, 2013). We initially expected membrane depolarization due to edema-induced compression ischemia in POEMS syndrome, and nerve edema detected by ultrasound partly correlated with axonal excitability. However, a combination of the nerve excitability changes did not support axonal depolarization. Different from an acute compression/ischemia model, compensatory mechanisms in response to depolarization might act, leading to resulted in a steady state during chronic exposure of VEGF and nerve edema. Our study did not reach a conclusion on whether membrane potential is altered in POEMS syndrome, because multiple factors in POEMS syndrome such as demyelination, and cytokine activation would also largely affect membrane properties.

There are several limitations in this study. We could examine sequential changes in a small number of patients ($n = 9$) and relatively short period of follow-up (3 months). Secondly, both nerve excitability testing and ultrasound works only in the restricted portion of the nerve (e.g., superficially located portion of the nerve). Finally, among the inflammatory cytokines elevated in POEMS syndrome, only VEGF was measured. The effects of cytokines should be evaluated as a network based on measurements of multiple cytokines.

The pathophysiology of POEMS neuropathy is still unclear, and a complex interaction of multiple factors could contribute to development of neuropathy in POEMS syndrome. Further multidisciplinary approach using electrophysiological, morphological, and biochemical methodology would be required to elucidate the pathogenesis of peripheral neuropathy in POEMS syndrome, and we would like to do so in future studies.

Potential financial interest

None.

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Conflict of interest: None.

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免疫性神経疾患　Crow-Fukase(POEMS)症候群
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免疫性神経疾患

—基礎・臨床研究の最新知見—

IV. 免疫性末梢神経疾患

Crow-Fukase（POEMS）症候群

桑原　聡

Crow-Fukase(POEMS)症候群

Crow-Fukase(POEMS) syndrome

桑原 聡

Key words：Crow-Fukase症候群，POEMS症候群，血管内皮増殖因子，自己末梢血幹細胞移植，サリドマイド

はじめに

Crow-Fukase症候群は末梢神経障害(多発ニューロパチー)を中核として浮腫・胸腹水，皮膚症状(剛毛・色素沈着，血管腫)，骨硬化病変，Mタンパク血症などを呈する全身性疾患である[1]．その病態の基盤として形質細胞の単クローン性増殖(plasma cell dyscrasia)と血管内皮増殖因子(VEGF: vascular endothelial growth factor)を中心とするサイトカインの過剰産生が想定されている．我が国では報告者の名前をとってCrow-Fukase(深瀬)症候群と呼ばれるが[2]，欧米では主要症状の頭文字をとってPOEMS(polyneuropathy，organomegaly，endocriopathy，M-protein，and skin changes)症候群と呼ばれることが多い[1]．かつては高月病(Takatsuki's disease)，PEP(polyneuropathy，edema，and plasma cell dyscrasia)症候群とも称されたがこれらはすべて同一の疾患である．Crow(1956年)，深瀬(1968年)による記載以来，特に我が国から多数の報告がなされてきた．従来は副腎皮質ステロイド，メルファランなどのアルキル化薬による治療が行われきたが，平均生存期間は数年であり，予後不良の疾患であった[2]．しかし2000年以降に，自己末梢血幹細胞移植を伴う大量化学療法，サリドマイド療法の導入により，その生命予後・機能予後は飛躍的に改善している．本症候群の病態は十分に明らかにされていないが，形質細胞をターゲットとした治療が有効であることが示されてきている．

本稿では治療の進歩を中心に本症候群について概説する．

1 疫　学

本症候群は稀少疾患であり2003年に行われた厚生労働省'免疫性神経疾患に関する調査研究班'によって行われた全国調査によると全国の患者数は約340人と推定されている[3]．しかしいまだ本症候群の認知度は高いとはいえず，診断されずに見逃されて患者も多いことが予想されている．実際の有病率はより高い可能性があり新たな全国調査が予定されている．男女比は1.5：1であり男性の罹患が多い．発症は20歳代から80歳代と広く分布しており，平均発症年齢は約48歳である．欧米からの報告よりも，日本からの報告が多く，東アジアにおいてより頻度の高い疾患であるとされている．日本国内において疾患の地域性は認められていない．

Satoshi Kuwabara: Department of Neurology，Graduate School of Medicine，Chiba University　千葉大学大学院医学研究院 神経内科学

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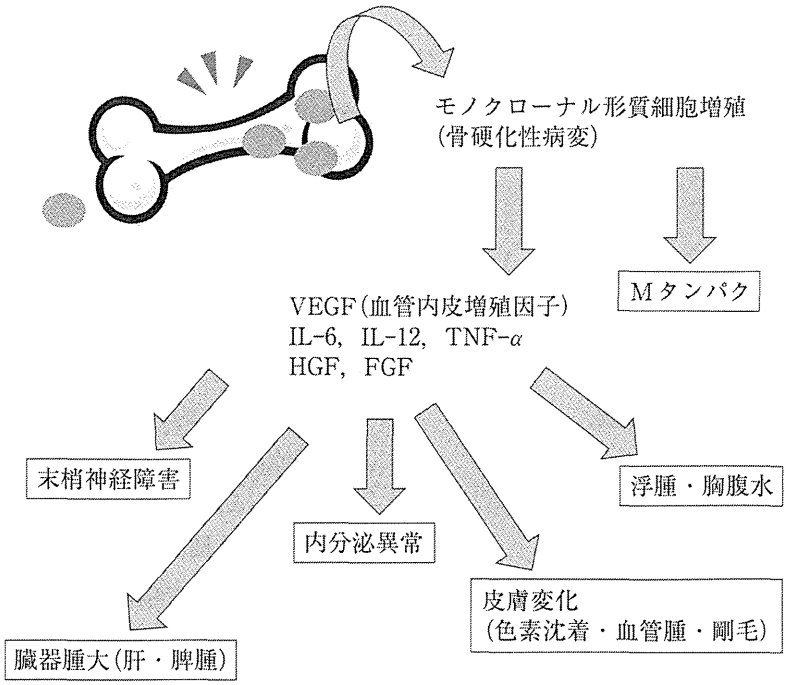

図1 POEMS症候群の病態

2 病因・病態

1996年に鹿児島大学の研究グループにより本症候群患者血清中においてVEGFが著明に増加していることが報告された[4]. VEGFは強力な血管新生, 血管透過性亢進作用をもつことから, 本症候群における浮腫, 臓器腫大, 血管腫などの臨床症状を説明しやすく, 病態と深く関連すると考えられている[1,4]. 本症候群の病態の基盤にあるのが形質細胞の単クローン性増殖であり, 恐らく異常形質細胞から分泌されるVEGFを中心とする各種サイトカインの過剰産生が特異な臨床症状を惹起していることが想定されている(**図1**).

本症候群では認められる血清Mタンパクの軽鎖はほとんどがラムダ鎖であり, その可変領域のgerm-lineにおいて免疫グロブリン軽鎖は特定のVλsubfamily遺伝子をもつことが示されている[5]. すなわち本症候群における免疫グロブリン軽鎖は特定のVλsubfamily遺伝子を有しており, この配列をもつMタンパクが産生された場合に本症候群が発症することになる. 分子病態の解明については更なる検討を要する.

VEGFの血管透過性亢進, 血管新生作用は, 浮腫, 胸腹水, 皮膚血管腫, 臓器腫大などを説明しやすいが, 末梢神経障害の発症機序については明らかにされていない. VEGFの血管透過性亢進により血液神経関門が破綻し, 炎症性サイトカインや神経毒性をもつ血清タンパクが神経実質に移行することや, 神経血管内皮の変化を介して神経の虚血が起こることなどが末梢神経障害の機序として推定されている. 神経生検における基本的な病理学的変化は脱髄(myelin uncompaction)であるが, 下肢遠位部では軸索変性が認められる.

3 診断と鑑別診断

本症候群患者の約半数は多発ニューロパチーで発症し, 残りの半数は浮腫, 胸腹水, 男性の場合には女性化乳房での発症があり初診する診療科は多岐にわたっている. 検診あるいは他疾患のための受診時に胸水・腹水, Mタンパク, クレアチニン高値, 骨硬化性病変が発見されることもある[2]. 早期診断・治療のためには各診療科においてこの疾患の可能性が常に考慮される必要がある. '治療可能な見逃してはならない疾患'として認識されるべきである. 疾患の

表1 Crow-Fukase症候群の診断基準
（Misawa S, Kuwabara S: Clin ExpNeuroimmunol 4: 318-325, 2013. より引用）

大基準	
	多発ニューロパチー（必須項目）
	血清VEGF高値
	Mタンパク
小基準	
	骨硬化性病変
	キャッスルマン病
	臓器腫大
	浮腫，胸水，腹水，心嚢水
	内分泌異常*
	皮膚異常
	乳頭浮腫
	血小板増多

definite：大基準3項目＋小基準1項目以上，probable：ニューロパチーと血清VEGF上昇＋小基準1項目以上，possible：大基準のうちニューロパチー＋小基準を2項目以上．
*甲状腺機能異常，糖尿病については有病率が高いため単独の異常では小基準の1項目として採用しない．

進行に伴い複数の症状が出現してくるが，早期診断のためには初診時に本症を念頭に置いた体系的検索を行う必要がある．

表1に現在提唱されている血清VEGF値を含めた診断基準を示す．大基準である多発ニューロパチーと血清VEGF高値は全例に存在する．また90％以上の患者にはMタンパクが認められる．多発ニューロパチーで発症し，初診の際に浮腫，皮膚症状が認められることが多く，この場合には比較的診断は容易であるが，小基準に含まれる多彩な症状のどれかで初発した際に本症の可能性を念頭に置くことが重要であり，神経症状の評価（多発ニューロパチーの有無），血清VEGF・Mタンパクの測定を行う．自覚症状に挙げられていなくても浮腫・皮膚症状は存在することが多い．

多発ニューロパチー発症の場合に，神経伝導速度の低下から慢性炎症性脱髄性多発ニューロパチー（CIDP）と診断され，免疫グロブリン，副腎皮質ステロイドによる治療が奏効せず，その後Crow-Fukase症候群と判明する症例が多く存在する．脱髄性ニューロパチーの観点からも本症を念頭に置いておく必要がある．

4 治 療

本症候群ではMタンパクに代表される形質細胞の単クローン性増殖が存在することから，治療の標的は異常増殖している形質細胞であると考えられる．1980年代までは主に副腎皮質ステロイドが治療として用いられていたが，平均生存期間は約3年と生命予後は不良であることが報告されていた[2]．1990年代には長期メルファランによる化学療法が導入され生存期間は5-10年に延長した[6]．本症候群の治療法は基本的に，同様に形質細胞の増殖性疾患である多発性骨髄腫の治療を応用する形で進められてきた．多発性骨髄腫の標準的治療が自己末梢血幹細胞移植を伴う大量化学療法，サリドマイド・レナリドマイド（lenalidomide），プロテアソーム阻害薬に移行しつつあることを受けて，本症候群に対する治療も変遷している[7]．特に2000年代に入って行われ始めた，幹細胞移植を伴う大量化学療法は長期寛解を目指す新規治療法として認められている．しかし治療関連死のリスクがあり，再発率を含めた長期予後は確立しておらず，今後の検討課題である．移植療法は高齢者や多臓器病変（特に腎障害）を有する患者には移植療法は施行できないため，移植適応にならない場合の治療法としてサリドマイド療法が期待されている．

1）自己末梢血幹細胞移植療法を伴う大量化学療法

本症候群に対しての移植療法の第1例目は1998年にイスラエルで行われた[8]．2000年代に入ってから報告が相つぎ，現在（2015年3月）までに，約60例の施行例が報告されている[9-11]．ほとんどの症例では諸症状の劇的な回復と血清VEGF値の正常化が認められている（**図2**）．3-5％に治療関連死がみられることが大きな問題点と思われるが，治療後の症状改善は従来療法より明らかに良好である[12]．末梢神経障害によるADL障害が高度な場合には積極的に移植療法を行うべきと考えられる．ADL障害が軽い場

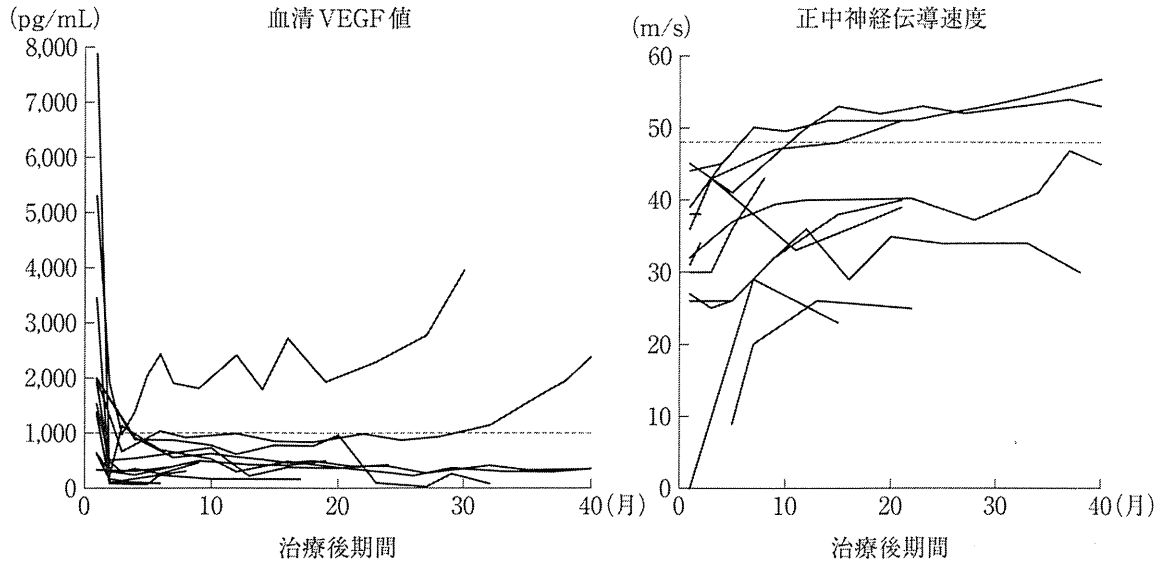

図2 自己末梢血幹細胞移植後の血清VEGF値、神経伝導速度の変化(文献[12]より改変)
点線は正常値を示す.

合には症例の状態に応じて移植可能な状態であっても後述するサリドマイド療法などの他の治療法で経過をみるという選択も行われるようになっている.

移植療法の適応としては年齢と多臓器障害の程度が最も大きい因子である. 年齢に関しては'適応は65歳以下'が暫定的なコンセンサスである. さらに'重篤な臓器障害を有さないこと'が適応の条件とされる. 66歳以上である場合には移植の適応にならないが, 65歳以下であっても臓器不全, 特に腎機能障害や大量の胸腹水のために治療関連死のリスクが高いと考えられる場合には適応とはならない.

2) サリドマイド療法

サリドマイドは我が国では1960年に発売され, その催奇形性によって製造は中止された. しかしその後血管新生抑制作用, 抗サイトカイン(TNF-αなど)作用などが明らかになり, ついで多発性骨髄腫における有効性が明らかにされた. 本症候群におけるサリドマイド治療は, これまで2例の症例報告と9症例におけるオープン試験が報告されている[13]. いずれの報告においても腹水, 呼吸不全, 末梢神経障害の改善がみられており, オープン試験では血清VEGF値の低下が示されている(**図3**). サリドマイドは形質細胞増殖抑制とともにVEGF産生を直接抑制すると考えられており, 本症に対して期待の大きい治療法といえる. 蓄積毒性として, 末梢神経障害があり, 本症候群では末梢神経障害は主症状であるため, その発現には十分注意する必要がある. また移植適応例であっても症状が軽度の場合にサリドマイド療法が第一選択になる可能性も考えられる. サリドマイドのアミノ酸置換誘導体であるレナリドマイド有効性も報告されている[14].

サリドマイド療法に関してはプラセボ対照・多施設共同群間比較試験が医師主導治験として2010年9月から開始され, 現在(2015年2月)承認に向けての結果解析中である.

3) 抗VEGFモノクローナル抗体

ベバシズマブは抗VEGFモノクローナル抗体で, 血管新生阻害作用による抗腫瘍効果を有し, 我が国では2007年に'治癒切除不能な進行・再発の結腸・直腸癌'の治療薬として製造販売承認を受けた. ベバシズマブの本症候群患者への報告例において有効性について結論は得られていない[15]. ただしこの治療によりVEGFの低下は非常に急速に認められるため, 胸・腹水や腎機能障害の進行が亜急性にみられた場合に, 救済的に併用する価値はある可能性がある.

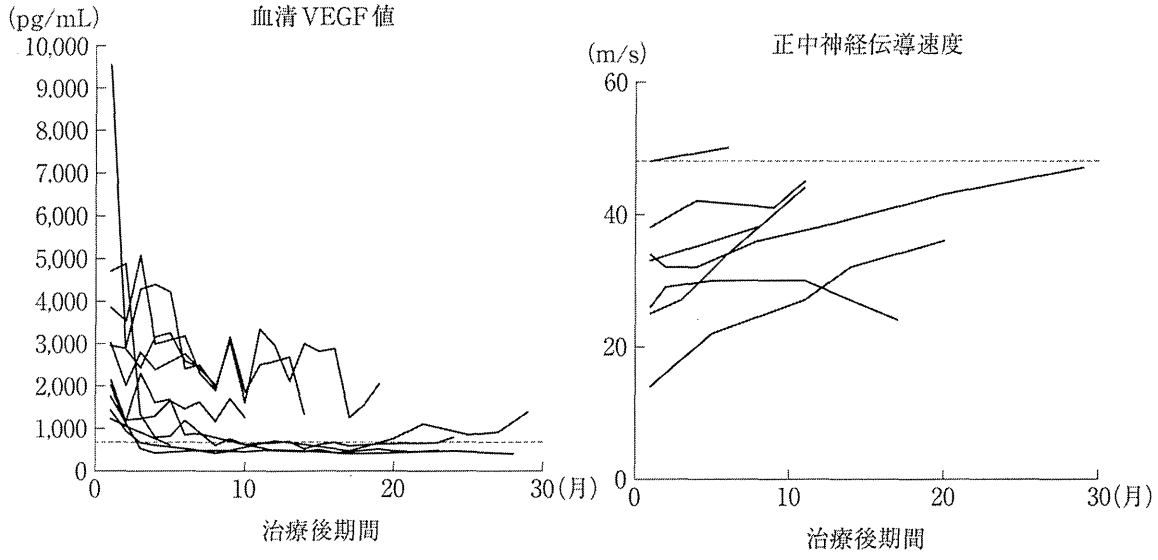

図3　サリドマイド療法後の血清VEGF値と神経伝導速度の変化（文献[13]より改変）
点線は正常値を示す．

おわりに

Crow-Fukase症候群の治療戦略は多発性骨髄腫領域における新規治療のめざましい発展により，国際的には移植療法，サリドマイドだけでなく，レナリドマイド，ボルテゾミブ，ベバシズマブと発展している．一方で，日本国内ではいずれの治療も保険適応がないため，各医療機関の体制により提供できる治療の選択肢が異なり，治療の較差が生じているのが現状である．しかし，適応外使用の継続は事態の改善にはつながらない．現在，進行中のサリドマイドの有効性に関する治験は医師主導のプラセボ対照ランダム化群間比較試験であり，稀少疾病であってもエビデンスの構築をめざしている．今後治療の選択肢が増え，本症候群の予後がさらに改善することが望まれる．

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