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LETTER TO THE EDITOR

Mobilization of PBSCs in poor mobilizers with POEMS syndrome using G-CSF with plerixafor

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Auto-SCT has been established as an effective treatment for patients with hematological malignancies such as lymphoma or myeloma. Unfortunately, some patients fail to mobilize a sufficient number of PBSCs for transplantation. Plerixafor is the first molecule to reversibly inhibit the binding of chemokine stromal cell-derived factor-1α (SDF-1α) to its cognate receptor, CXCR4.[1] Many recent reports have shown that there is a potential clinical application for plerixafor in PBSC harvesting.[2–6]

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal component and Skin changes) syndrome is a rare paraneoplastic syndrome secondary to plasma cell dyscrasia. As this disease is rare, no standard treatment has been developed. However, treatment options for this syndrome, such as the use of thalidomide, lenalidomide, bortezomib and bevacizumab (an antivascular endothelial growth factor (VEGF) Ab), have increased in the past decade. To date, high-dose melphalan followed by auto-SCT has been demonstrated to be the most effective treatment strategy.[7,8] However, patients with poor mobilization cannot undergo auto-SCT. In addition, PBSC harvesting in patients with this syndrome is challenging, and these patients are at a higher risk than those with other hematological malignancies, because of poor performance status, morbidities associated with uncontrollable effusions and splenomegaly.[7] Here, we report two poorly mobilized cases of POEMS syndrome in which PBSCs were successfully harvested using G-CSF with plerixafor.

Case 1

A 43-year-old man was diagnosed with POEMS syndrome (IgA-λ) and was referred to Chiba University Hospital in June, 2009. On admission, he was diagnosed with severe ascites, pleural effusion and neuropathy. His performance status was 4. He was treated with a combination therapy of thalidomide (300 mg/day), prednisolone and bevacizumab (5 mg/kg), which facilitated improvement in the systemic edema. PBSC harvesting was attempted using G-CSF alone (lenograstim; 10 μg/kg, 5 days) in June, 2010 using a blood cell separator (COBE Spectra, CaridianBCT, USA) for 4 h for each collection. However, the percent of $CD34^+$ cells of the apheresis products were only 0.1% on day 5 and 0.04% on day 6, and we failed to harvest sufficient stem cells (Figures 1 and 2). A second PBSC harvest was planned 1 month later using G-CSF alone at the same dosage as the first collection after reducing thalidomide to 200 mg/day, but we failed to harvest sufficient $CD34^+$ cells ($CD34^+$% of the product: 0.05%). A third attempt to harvest PBSC using G-CSF 10 μg/kg in combination with plerixafor was planned under thalidomide 200 mg/day. Plerixafor (240 μg/kg) was administered s.c. 11 h before apheresis. The percent of $CD34^+$ cells of the apheresis products from day 5 through day 8 were 0.2%, 0.25%, 0.33% and 0.17%, respectively, and we successfully harvested adequate $CD34^+$ cells (3.31×10^6/kg) over four apheresis procedures. There was no adverse event during PBSC harvesting. The patient underwent auto-SCT after a high dose of i.v. melphalan (100 mg/m^2), once daily on days 2 and 3 (total dose: 200 mg/m^2). Neutrophil and reticulocyte recoveries were recorded on days 16 and 13, respectively. Platelet recovery has not been more than 5×10^4/μL at the time of writing.

Case 2

A 55-year-old man with POEMS syndrome (IgG-λ) was referred to our institution for auto-SCT, with ascites, pleural effusion, muscle weakness and neuropathy. His performance status was 4. He was treated with thalidomide (300 mg/day) and prednisolone, which facilitated improvement in the systemic edema and effusions. PBSC harvesting was attempted using G-CSF alone (10 μg/kg, 5 days). After the administration of G-CSF, his WBC count markedly increased and G-CSF dose was reduced. The WBC count had increased to 53 200/μL by day 5, but the percent of $CD34^+$ cells of the apheresis products on day 5 was only 0.05% and we could not harvest sufficient $CD34^+$ cells (Figures 1 and 2). We then planned a PBSC harvest using G-CSF (5 μg/kg, 5 days) and plerixafor under the same dose of thalidomide. Plerixafor was administered using the same protocol as in Case 1. We successfully collected adequate PBSCs (total $CD34^+$ cells: 5.05×10^6/kg) over 2 days of apheresis procedures ($CD34^+$% of the apheresis products: 0.2% on day 5 and 0.35% on day 6). The patient underwent auto-SCT following high-dose melphalan (200 mg/m^2) in September, 2011. Neutrophils, reticulocytes and platelets were recovered on days 15, 18 and 15, respectively.

We successfully harvested PBSC in both patients using G-CSF with plerixafor. The apheresis procedures were safe, with no adverse events, and hematopoietic recovery was prompt. SDF-1α is a key factor in the homing of hematopoietic stem cells to BM, and is constitutively expressed in the BM microenvironment. Its receptor has been shown to be the chemokine receptor, CXCR4. Plerixafor is the first direct reversible antagonist of SDF-1α. Pharmacological inhibition of CXCR4 by plerixafor enhances the release of hematopoietic stem cells into the peripheral blood.[1]

Perea *et al.*[9] reported that ~20% of patients with myeloma could not mobilize sufficient PBSC for auto-SCT with G-CSF alone

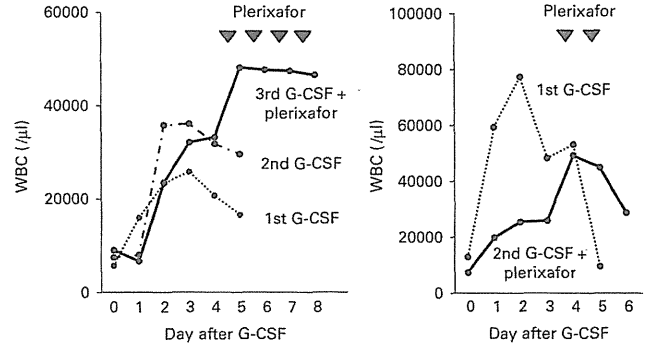

Figure 1. Clinical course of PBSC harvesting in two cases (Cases 1 and 2) with POEMS syndrome. Dashed lines indicate WBC count with G-CSF alone and bold lines indicate WBC count with G-CSF and plerixafor.

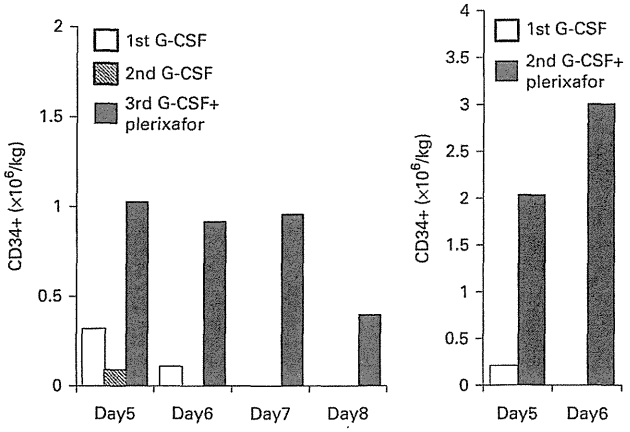

Figure 2. The number of $CD34^+$ cells/kg on each day of PBSC harvesting in Cases 1 and 2. Open or dashed bars indicate the number of $CD34^+$ cells/kg of the each apheresis products harvested with G-CSF alone and solid bars indicate WBC count with G-CSF and plerixafor.

or G-CSF with chemotherapy. The rate of poor mobilization in POEMS syndrome in our institution was approximately the same (5/24, 21%). Suitable PBSC harvesting should be performed to facilitate optimum timing of safe and successful auto-SCT in patients with POEMS syndrome. We were able to harvest significantly higher numbers of $CD34^+$ cells in patients with POEMS syndrome using high-dose CY than with G-CSF alone.[10] However, these patients are at a higher risk during chemotherapy with high-dose CY than with G-CSF alone, and PBSC harvesting with high-dose CY is challenging because of poor performance statuses. Dispenzieri *et al.*[7] reported a case requiring intubation during PBSC harvesting. As the number of plasma cells in BM is low, chemotherapy is not always necessary before PBSC harvesting in POEMS syndrome compared with lymphoma or myeloma. Therefore, G-CSF monotherapy would be a suitable regimen for safe and efficient PBSC harvesting in these patients. As auto-SCT is an effective and pivotal treatment for this particular syndrome, plerixafor combined with G-CSF is a safe and effective strategy for poor mobilizers with G-CSF.

Recently, we analyzed factors associated with the efficiency of PBSC collection in POEMS syndrome patients undergoing auto-SCT and reported that splenomegaly was associated with a decrease in the efficacy of PBSC collection but VEGF was not.[10] Case 1 had huge splenomegaly before PBSC collection and it might have caused poor mobilization. The patient had poor platelet engraftment although enough number of $CD34^+$ cells was infused. As the patient had persistent splenomegaly even after auto-SCT, it might be related to the prolonged thrombocytopenia. Case 2 did not have splenomegaly before PBSC harvest. His WBC count rapidly increased after G-CSF injection, but the number of $CD34^+$ cells was low. As the patient had no history of chemotherapy except for thalidomide, there has been no obvious reason why Case 2 was a poor mobilizer.

In conclusion, plerixafor combined with G-CSF is safe and useful in poor mobilization patients with POEMS syndrome. Safe and efficient harvesting of PBSC with appropriately timed auto-SCT could improve the prognosis and quality of life in these patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Preserved autonomic function in patients with POEMS syndrome

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ABSTRACT

Aim: We systematically performed autonomic testing on patients with polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes syndrome (POEMS) to determine whether autonomic function is preserved in such patients.
Methods: We studied 17 POEMS patients, 17 diabetic neuropathy (DN) patients and 17 age-matched normal subjects. Blood pressure responses to the head-up tilt test and heart rate variability were used to evaluate cardiovascular autonomic function. Sweat responses and cutaneous vasoconstriction to several stimuli were recorded via the finger tips to estimate cutaneous sympathetic function. In addition, motor nerve conduction studies were performed.
Results: Although the results of the autonomic testing were normal in POEMS patients, motor disability was severe, and motor nerve conduction studies provided evidence of extensive axonal loss. The DN patients showed significantly impaired autonomic responses despite mild motor dysfunction.
Conclusions: Autonomic function was normal in POEMS patients, indicating the preservation of autonomic fibers and selective involvement of large fibers.

1. Introduction

Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes syndrome (POEMS) is a disease that causes mixed axonal/demyelinating polyneuropathy with multiple organ involvement and plasma cell dyscrasia. Its major clinical feature is chronic progressive polyneuropathy with predominant distal motor disability [1–3], which is presumably mediated by the overproduction of vascular endothelial growth factor [4]. POEMS syndrome is potentially fatal [2], and immediate treatment, such as using high-dose chemotherapy with autologous peripheral blood stem cell transplantation or thalidomide therapy, is usually required [5,6]. However, early diagnosis is quite difficult, particularly when patients present with polyneuropathy without the associated systemic symptoms or signs such as hyperpigmentation of the skin, peripheral edema, hypertrichosis or organomegaly [7]. In POEMS, motor involvement follows the sensory symptoms which begin in the feet. Sensory and motor symptoms are distal, symmetric and progressive with a gradual proximal spread [7]. Information on the extent of autonomic involvement in this syndrome may be helpful for its early diagnosis. However, no previous reports have focused on autonomic function in patients with POEMS. Therefore, we performed systematic autonomic testing in POEMS patients and compared the results with those in patients with diabetic neuropathy (DN).

2. Methods

We prospectively studied 17 POEMS patients (13 men and 4 women; mean age, 54 ± 9 years; mean disease duration, 3 ± 3 years) in this study. They were consecutive patients who were referred to the Department of Neurology of Chiba University Hospital from 2005 to 2009. All patients fulfilled the published diagnostic criteria for POEMS that were proposed by Dispenzieri. Table 1 shows the clinical profiles of our POEMS patients. Seventeen patients with DN (11 men and 6 women; mean age, 60 ± 10 years; mean disease duration of diabetes, 13 ± 11 years) were included as disease controls. DN was defined by known diabetes mellitus criteria and the presence of symmetric sensory-dominant polyneuropathy [8]. The mean hemoglobin A1c levels in DN patients were 8.3% ± 1.6%. Seventeen healthy controls (13 men and 4 women; mean age, 55 ± 9 years) were also evaluated. No participant received medications that could affect autonomic nervous system activity. Written informed consent was obtained from all patients. The ethics committee of Chiba University School of Medicine approved this study.

Clinical motor disability was assessed using the following overall neuropathy limitation scale: a grade for each upper limb was scaled from 0 (normal) to 5 (most severe) and that for each lower limb was scaled from 0 (normal) to 7 (most severe) [9]. Motor nerve conduction studies were performed on the tibial nerve using conventional procedures with a lower limit of 5.6 mV for the normal range of compound motor action potentials (CMAPs) according to our laboratory data. Autonomic function tests were performed in a quiet room at an ambient temperature of 24–26 °C. Each subject was asked to relax, stay awake

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Table 1
Clinical profiles of patients with POEMS syndrome.

No.	Age (years)	Sex	Disease duration (months)	ONLS		Sensory loss		CMAP* (mV)	SNAP** (μV)	VEGF† (pg/mL)	Therapeutic response		
				Upper limb	Lower limb	Pain	Vibration				Steroid	Thalidomide	Auto-PBSCT
1	43	M	15	1	3	Mild	Severe	NR	NR	7160			
2	58	M	5	0	2	Mild	Severe	2.9	3.7	2040			
3	52	M	44	3	6	Severe	Severe	NR	NR	378	NTR		
4	41	M	7	1	2	Severe	Severe	NR	NR	5110			
5	50	M	34	2	3	Mild	Mild	NR	NR	317	PTR	PTR	TR
6	34	F	48	1	7	Mild	Moderate	NR	10	3990			
7	63	M	49	1	1	Mild	Severe	1.1	NR	470	NTR	NE	
8	55	M	27	2	3	Mild	Mild	0.32	4	499			TR
9	57	M	13	1	4	Mild	Severe	NR	NR	4810	NE	NE	
10	64	F	44	1	2	Severe	Severe	0.15	NR	5570	PTR	NE	
11	46	F	13	2	4	Severe	Severe	NR	NR	9950	NE	NE	
12	57	M	11	1	3	Moderate	Moderate	NR	2	5250			
13	59	M	29	0	3	Mild	Severe	NR	NR	320		PTR	TR
14	53	M	126	0	0	Mild	Mild	NR	7	261	PTR		TR
15	53	M	55	1	2	Mild	Severe	0.5	NR	1310	PTR	PTR	TR
16	65	M	64	1	4	Moderate	Moderate	NR	NR	119	PTR	NE	
17	51	F	52	1	2	Mild	Mild	NR	NR	450	PTR		TR

POEMS = polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes syndrome.
ONLS, overall neuropathy limitation scale (0 indicates no symptoms of neuropathy, most severe grades are 5 in the upper limb and 7 in the lower limb).
CMAP, compound motor action potential in the tibial nerve; SNAP, sensory nerve action potential in the sural nerve.
NR, not recorded; VEGF, vascular endothelial growth factor; Auto-PBSCT, autologous peripheral blood stem cell transplantation.
TR, therapeutic response; PTR, partial therapeutic response; NTR, no therapeutic response; NE, not evaluated.
*Normal > 5.6 mV, **normal > 3.4 μV, †normal < 1000 pg/mL.

and remain supine for at least 20 min before the tests. During the head-up tilt test, systolic and diastolic blood pressure and heart rate were measured using a sphygmomanometer at 1-min intervals. After 5 min of baseline measurements, each subject was tilted to 70° for 10 min on an electrically driven tilt table. Electrocardiography was used to record limb lead (II) measurements during normal breathing in the supine position, and three series of 100 successive R–R intervals were used to obtain the coefficient of variation of the R–R intervals (CV_{R-R}). This coefficient was calculated as the standard deviation divided by the mean R–R interval (%). The average of these three series was used as the CV_{R-R} value. Sweat output was measured on the right thumb fingertip using a sudorometer (model SKD-1000; SKINOS Co., Nagano, Japan), and cutaneous blood flow was recorded on the right index finger tip using a Doppler flow meter (model ALF21D; Advance, Tokyo, Japan). Sweat output and skin blood flow were recorded during a sympathetic activation test that involved deep inspiration, mental arithmetic and exercise. These procedures increased sweat output (sympathetic sweat response) and reduced cutaneous blood flow (skin vasomotor reflex) to the palms [10]. The amplitude of the sympathetic sweat response was measured from the baseline to the peak. The amplitude of the skin vasomotor response was calculated as the percentage of blood flow that fell below the basal blood flow rate (reduction rate).

Analysis of variance (ANOVA) was used to analyze the differences in the parametric values among all three groups. When ANOVA showed a significant difference, a Tukey's test was performed. A Chi-square test or the Mann–Whitney *U*-test was used to analyze differences between the two patient groups. Values were presented as means ± standard deviation.

3. Results

The overall neuropathy limitation scale scores (arm grade = 1.1 ± 0.8, leg grade = 3.0 ± 1.7) for the POEMS patients were significantly higher than those (0.4 ± 0.5, 0.2 ± 0.7, respectively) for the DN patients ($p<0.01$, $p<0.000005$, respectively). In the tibial nerve, CMAPs were absent in 12 (71%) and reduced in five (29%) POEMS patients; none demonstrated normal CMAPs. In the DN group, CMAPs were reduced in nine (53%) and normal in eight (47%) patients; none demonstrated absent CMAPs. The CMAP reduction in the POEMS patients was significantly greater than that in the DN patients ($p<0.05$).

In the head-up tilt test, blood pressures and heart rate in the supine position were comparable between the three groups. None of the patients showed serious bradycardia (heart rate < 50 beats/min) or tachycardia (heart rate > 100 beats/min) in the supine position. One POEMS patient (6%) and 12 DN patients (71%) showed orthostatic hypotension (decrease in systolic blood pressure of > 20 mm Hg or decrease in diastolic pressure of > 10 mm Hg) during the head-up tilt test [11]. The decreases in systolic and diastolic blood pressures recorded during the head-up tilt test were significantly greater in the DN group than those in controls ($p<0.0005$, $p<0.01$, respectively) and POEMS patients ($p<0.0005$, $p<0.001$, respectively); they were not significantly different between POEMS patients and controls. One POEMS patient (6%) and seven DN patients (41%) showed abnormal CV_{R-R} values. The CV_{R-R} values in the DN patients were significantly lower than those in the POEMS patients ($p<0.05$), whereas they were not significantly different between POEMS patients and controls (Fig. 1).

Basal sweat output was comparable between the three groups. Two POEMS patients (12%) and seven DN patients (41%) did not show sympathetic sweat responses to any stimuli. The amplitudes of the sympathetic sweat responses in the DN patients were significantly lower than those in the controls for deep inspiration ($p<0.01$), mental arithmetic ($p<0.05$) and exercise ($p<0.05$), and they were also significantly lower than those in the POEMS patients for mental arithmetic ($p<0.05$) and exercise ($p<0.05$). There were no significant differences between the POEMS and control groups (Fig. 2). The baselines of cutaneous blood flow were comparable between the three groups. Six DN patients (35%) did not show skin vasomotor responses to any stimuli, whereas all POEMS patients presented normal responses. The reduction rates of the skin vasomotor responses in the DN patients were significantly lower than those in the controls for deep inspiration ($p<0.001$) and significantly lower than those in the POEMS patients for deep inspiration ($p<0.001$) and exercise ($p<0.05$). The reduction rates of the skin vasomotor responses were not significantly different between the POEMS and control groups (Fig. 2).

4. Discussion

In our study, POEMS patients had high disability scores and severe motor neuropathies that were demonstrated by nerve conduction studies. However, most showed normal results on the cardiovascular

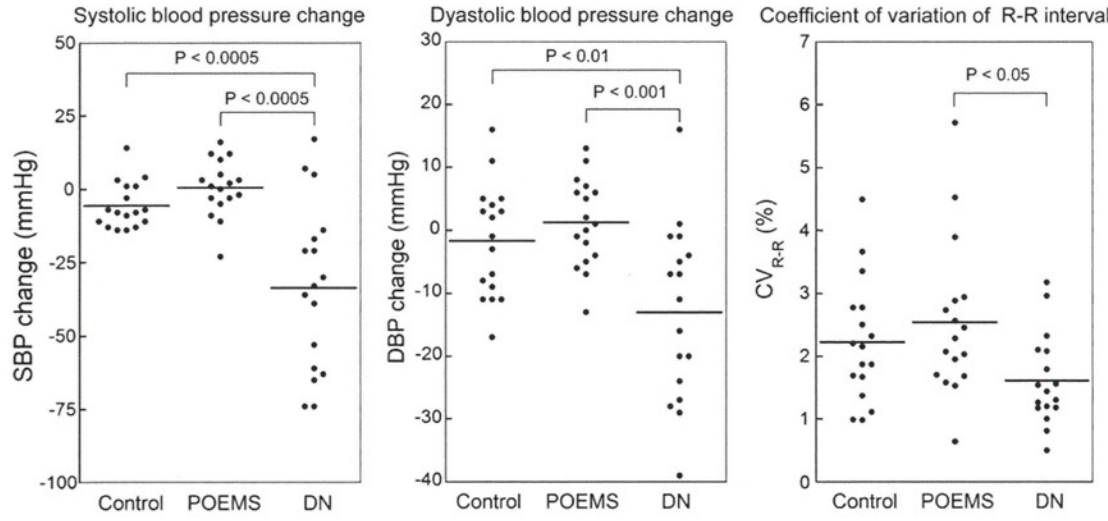

Fig. 1. Changes in SBP (left) and DBP (middle) during the head-up tilt test and CV_{R-R} (right). SBP = systolic blood pressure, DBP = diastolic blood pressure, CV_{R-R} = coefficient of variation of the R–R interval, POEMS = polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes syndrome, DN = diabetic neuropathy.

and cutaneous sympathetic function tests. These findings suggest that autonomic fibers may be preserved despite major involvement of the large motor fibers in POEMS patients. The neuropathological findings in these patients are reportedly characterized by a mixture of demyelination and axonal degeneration of A fibers and segmental demyelination with uncompacted myelin lamellae. Axonal degeneration of the distal nerve segments is also frequently observed [4,12,13]. This suggests the primary involvement of the myelin sheath with secondary axonal or Wallerian degeneration in POEMS patients. Previous histological studies of the sural nerves in POEMS patients have shown preserved

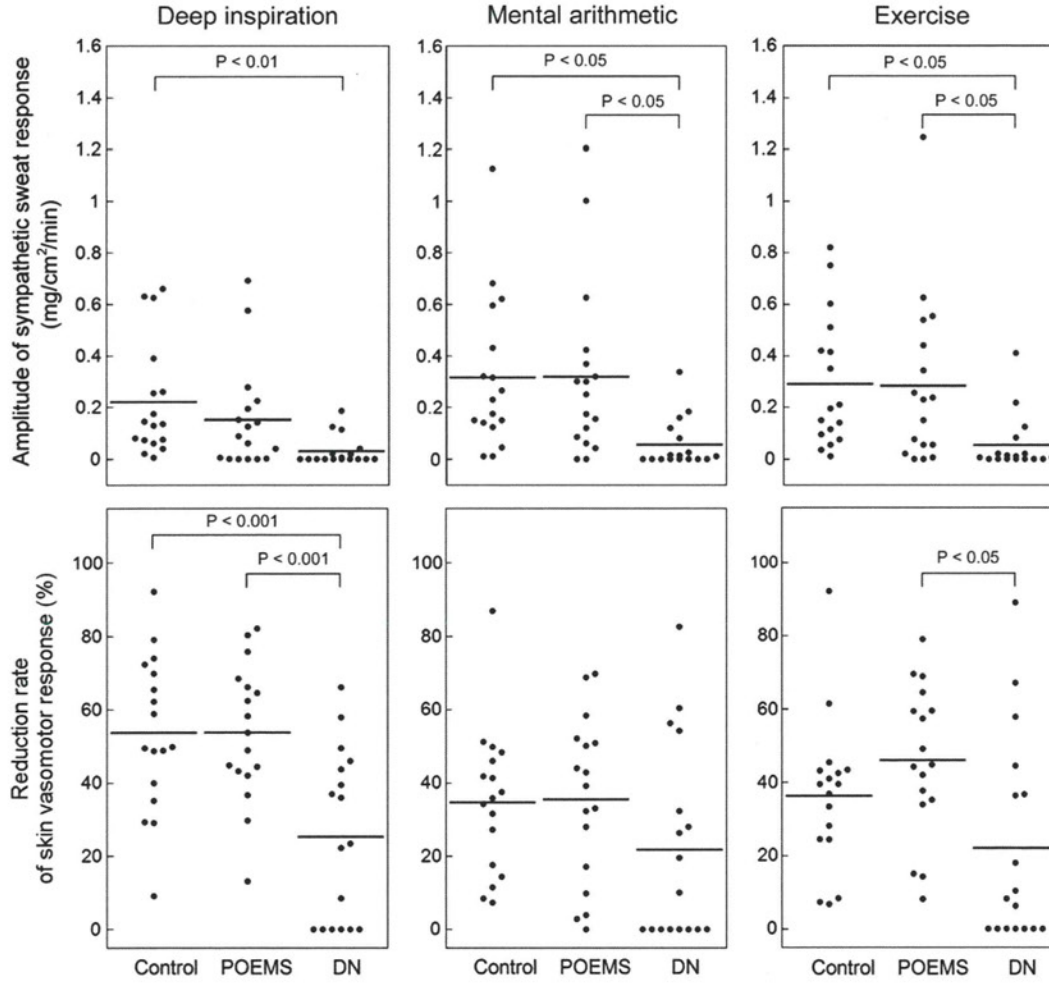

Fig. 2. Amplitudes of sympathetic sweat responses (upper) and reduction rates of skin vasomotor responses (lower) for deep inspiration (left), mental arithmetic (middle) and exercise (right). POEMS = polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes syndrome, DN = diabetic neuropathy.

unmyelinated nerve fibers despite the prominent loss of myelinated fibers [13]. Therefore, autonomic unmyelinated fibers may also be preserved in POEMS patients. However, these previous histological studies consisted of overall evaluations of unmyelinated fibers, and autonomic fibers were not specifically evaluated. An investigation of sudomotor nerve terminals in skin biopsies could selectively evaluate unmyelinated autonomic fibers, but there have been no pathological studies on the peripheral autonomic fibers in POEMS patients. To the best of our knowledge, this is the first study to clinically investigate autonomic function in POEMS patients, and the results indicated preserved autonomic fibers in these patients. POEMS patients may be initially diagnosed with diabetic polyneuropathy because they often have abnormalities in glucose metabolism because of endocrinopathy [14]. In our study, DN patients showed prominent autonomic dysfunction despite their low disability scores and mild motor neuropathy, which was in contrast to the POEMS patients. These findings indicated the predominant involvement of autonomic nerve fibers in DN patients. Other symmetrical sensorimotor axonal polyneuropathies, such as familial amyloid polyneuropathy, alcoholic neuropathy and nutritional neuropathies, may also be considered as differential diagnoses of POEMS. However, autonomic nerve fibers are involved in those axonal polyneuropathies [15]. Autonomic function tests may be helpful in differentiating POEMS from distal symmetrical axonal polyneuropathies such as DN.

Chronic inflammatory demyelinating polyneuropathy (CIDP) may be difficult to differentiate from POEMS, although the clinical characteristics and laboratory tests, including nerve conduction studies, are useful for separating these diseases. Typical CIDP shows motor dominant polyneuropathy with proximal and distal muscle weakness [16], whereas typical POEMS syndrome shows sensorimotor polyneuropathy with predominant distal weakness, particularly in the lower limbs [2]. With electrophysiological studies, POEMS patients tend to show slowing nerve conduction that is more predominant in the intermediate than in the distal nerve segments, rare conduction block and severe attenuation of CMAPs in the lower rather than in the upper limbs compared to CIDP patients [17]. However, POEMS patients may also have motor-dominant polyneuropathies with prolonged distal latencies and dispersion of CMAPs which is similar to CIDP patients [18]. Actually, a considerable number of POEMS patients have been reported to be initially diagnosed with CIDP [19]. In addition, while rare, POEMS may also resemble patients with Guillain–Barré syndrome (GBS) during acute or subacute courses [20]. Meanwhile, CIDP and GBS patients may have higher incidences of autonomic abnormalities compared with that found in our POEMS patients; it has been reported that 25%–76% of CIDP patients showed autonomic abnormalities [21,22], including orthostatic hypotension [22] and absent sympathetic skin response [21], and that approximately two-thirds of GBS patients have dysautonomia [23] including tachycardia [24,25], bradycardia [26,27], orthostatic hypotension [24,25] and absent sympathetic skin responses [28]. Dysautonomia may be a clinical red flag that requires careful diagnostic assessment of neuropathies other than POEMS, although it may not strictly distinguish them.

In our study, a certain number of DN patients showed normal results on the autonomic function tests as did the POEMS patients. Furthermore, orthostatic hypotension was found in 71% of our DN patients, which was higher than those found in previous reports on DN [29,30]. Diabetic patients with severe autonomic neuropathy may tend to visit our department (Neurology). Thus, there is a possibility that we recruited DN patients with severe autonomic neuropathy in this study. The sensitivity of the autonomic function tests might actually be somewhat lower for distinguishing POEMS from DN or other polyneuropathies.

POEMS syndrome should be considered as a differential diagnosis in patients who present with polyneuropathy with preserved autonomic function despite severe motor dysfunction.

Conflict of interest

None.

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RESEARCH PAPER

Different neurological and physiological profiles in POEMS syndrome and chronic inflammatory demyelinating polyneuropathy

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ABSTRACT

Background POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes) syndrome, a rare cause of demyelinating neuropathy associated with multiorgan involvement, has been increasingly recognised. Polyneuropathy is often an initial manifestation and therefore the disorder can be misdiagnosed as chronic inflammatory demyelinating polyneuropathy (CIDP).

Objective To elucidate whether POEMS syndrome and CIDP are differentiated based on profiles of neuropathy.

Methods Clinical and electrophysiological data were reviewed in consecutive POEMS syndrome (n=51) and typical CIDP (n=46) patients in a single Japanese hospital between 2000 and 2010.

Results Both POEMS and CIDP patients showed symmetric polyneuropathy, physiological evidence of demyelination (70% of POEMS patients fulfilled the electrodiagnostic criteria for definite CIDP) and albuminocytological dissociation; 49% of the POEMS syndrome patients had neuropathy onset and 60% of them were initially diagnosed as having CIDP by neurologists. Clinically, POEMS neuropathy more frequently showed severe leg pain (76% vs 7%; $p<0.001$), muscle atrophy (52% vs 24%; $p=0.005$) and distal dominant muscle weakness. Electrophysiologically, POEMS syndrome was characterised by less prolonged distal motor latency (mean 5.6 ms vs 8.1 ms; $p<0.001$) and higher terminal latency index (0.42 vs 0.33; $p=0.006$) in the median nerves, and unrecordable tibial and sural responses ($p<0.001$), suggesting demyelination predominant in the nerve trunk rather than in the distal nerve terminals, and axonal loss in the lower limb nerves.

Conclusions Before development of typical systemic manifestations, POEMS neuropathy can be distinguished from CIDP by the clinical profile and patterns of nerve conduction abnormalities. Recognition of these features leads to early diagnosis and proper treatment for POEMS syndrome.

INTRODUCTION

POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes) syndrome is a rare cause of demyelinating neuropathy associated with plasma cell dyscrasia and multiorgan involvement.[1–3] Serum levels of vascular endothelial growth factor (VEGF) are elevated in POEMS syndrome, and increased vascular permeability and neovasculisation mediated by VEGF are considered to cause characteristic symptoms.[4] POEMS syndrome has been increasingly recognised, and since 2000, over 400 reports have been published from Western and Asian countries.

POEMS syndrome is a serious disease with neurological disability due to progressive polyneuropathy,[5] with high mortality by multiorgan failure.[6 7] There are no randomised controlled trials for POEMS syndrome[8] but several case series have shown benefits of treatments such as high dose chemotherapy with autologous peripheral blood stem cell transplantation[9 10] and thalidomide therapy.[11]

In the advanced stage of POEMS syndrome, the diagnosis is not difficult; the specific combination of polyneuropathy, peripheral oedema, pleural effusion/ascites and skin changes would lead to the diagnosis that can be confirmed by the presence of M protein and elevated serum VEGF levels. However, approximately 50% of POEMS patients initially showed only polyneuropathy.[5] Because POEMS syndrome causes peripheral nerve demyelination, the electrodiagnostic findings may be similar to those of chronic inflammatory demyelinating polyneuropathy (CIDP). Previous studies suggest that patterns of nerve conduction abnormalities are different in the two disorders[12 13] but these studies included a small number of POEMS patients (eight and 12, respectively). Therefore, the findings are not conclusive and need to be confirmed.

Assuming that patients with POEMS syndrome and those with CIDP require fundamentally different treatments, the differential diagnosis is clinically important. In the past 10 years, we have experienced more than 10 POEMS patients who were initially misdiagnosed as suffering from CIDP by neurologists and received immunoglobulin therapy, resulting in no effects and progression of neuropathy. This led us to investigate whether POEMS syndrome is associated with particular patterns of clinical features and nerve conduction study results, and whether such profiles differ from those of CIDP.

METHODS

Patients

This study included 51 consecutive patients with POEMS syndrome (35 men and 16 women) seen at Chiba University Hospital (Chiba, Japan) between 2000 and 2010. Age ranged from 34 to 73 years (median 53 years). All patients fulfilled the diagnostic criteria of POEMS syndrome,[8] and had increased serum VEGF levels measured by ELISA. In

the same study period, there were 46 patients with typical CIDP (29 men and 17 women; median age 44 years) whose condition fulfilled the diagnostic criteria for typical CIDP proposed by the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS).[14] Clinical and electrophysiological data of both patient groups were analysed. A total 73 healthy subjects served as normal controls in nerve conduction studies. The study protocol was approved by the ethics committee of Chiba University School of Medicine.

Electrophysiology

Nerve conduction studies were performed using conventional procedures and by a Viking four electromyography machine. Motor nerve studies were made of the median, ulnar and tibial nerves, including F wave analyses. Terminal latency index (TLI) was calculated using the following formula:

TLI = terminal distance (mm)/(distal latency (ms) × conduction velocity (m/s)). Partial motor conduction block was defined as >50% reduction of compound muscle action potentials between the stimulus sites.[14] Antidromic sensory nerve conduction studies were performed in the median and sural nerves.

Statistical analyses

Differences in median values were tested using the Mann–Whitney U test. We compared positive and negative groups using Fisher's exact test for categorical outcomes. Receiver operating characteristic analyses were performed to calculate sensitivity and specificity. A p value of <0.05 was considered to be statistically significant. All statistical analyses were performed using the SAS software program, V.9.2 (SAS Institute Inc).

RESULTS

Clinical features

Of the 51 patients with POEMS syndrome, 25 (49%) showed polyneuropathy as an initial and isolated symptom, and in the remaining patients, foot oedema, skin pigmentation or gynaecomastia preceded neuropathy. In the former group with neuropathy onset, 15 (60%) were initially diagnosed as having CIDP by neurologists and received immunoglobulin treatment. Because of the lack of beneficial effects of immunoglobulin, they were referred to our hospital. The median delay to the correct diagnosis was 12 months, and during this period neurological disability worsened (median Hughes grade by 1; range 0–2), and other multiorgan involvement such as massive pleural effusion and cardiac failure developed in 10 patients.

Table 1 shows the clinical profiles of patients with POEMS syndrome and those with typical CIDP. The two patient groups showed symmetric polyneuropathy. POEMS patients showed distal dominant muscle weakness with amyotrophy, which was mainly seen in the lower extremities, whereas in CIDP patients proximal as well as distal muscles were involved and both upper and lower extremities were almost equally involved. Positive sensory symptoms were significantly different; POEMS patients had neuropathic pain in the distal lower limbs much more frequently, and this substantially disturbed the patients' quality of life. A few CIDP patients complained of pain that was generally mild.

Electrophysiology

Using the EFNS/PNS electrodiagnostic criteria, 70% of the POEMS syndrome patients fulfilled the criteria for definite CIDP.

Table 1 Clinical profiles of POEMS syndrome and CIDP patients

	POEMS (n=51)	CIDP (n=46)	p Value
Clinical profile			
Age (years)	53 (11)	44 (20)	**0.01**
M:F	35:16	29:17	0.6
Hughes grade	3 (1–4)	3 (2–4)	0.7
Time to Hughes grade 3 (months)	7 (1–50)	2 (1–6)	0.5
Neurological feature			
Cranial nerve palsy	2%	18%	**0.009**
MRC score			
Deltoid	5 (3–5)	4 (1–5)	**0.006**
Wrist extensor	5 (2–5)	4 (1–5)	**0.003**
Iliopsoas	4 (1–5)	4 (1–5)	0.4
Tibialis anterior	2 (1–5)	4 (1–5)	**0.03**
Muscle atrophy			
Upper extremity	37%	22%	0.1
Lower extremity	52%	24%	**0.005**
Sensory symptom			
Dysesthesia/paresthesia	98%	83%	**0.01**
Pain	76%	7%	**<0.0001**
Pain sensory loss	69%	83%	0.09
Vibratory sensory loss	96%	92%	0.8
Areflexia	98%	100%	0.9
CSF protein (mg/dl)	126 (73)	154 (163)	0.4

Data are expressed as mean (SD), median (range) or per cent.
CIDP, chronic inflammatory demyelinating polyneuropathy; MRC, Medical Research Council; POEMS syndrome, polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes syndrome.

Table 2 shows the results of nerve conduction studies. There were major differences, and compared with CIDP patients, POEMS patients showed less prolonged distal latency (p<0.0001) and higher TLI (p=0.006) in the median nerves, and more frequently unrecordable tibial compound muscle action potentials (56% vs 7%; p<0.0001). Receiver operating characteristic analyses showed a sensitivity of 0.85 and specificity of 0.67 for distal motor latency, and sensitivity of 0.93 and specificity of 0.62 for TLI. Apparent increases in distal compound muscle action potential duration (>9 ms) was found for 6% of POEMS patients and for 13% of CIDP patients. Motor nerve conduction velocities were similarly reduced in both patient groups. In sensory nerve studies, patients with POEMS syndrome had relatively preserved amplitudes of median sensory nerve action potentials but more severe involvement of sural sensory potentials (absent response 68% vs 36%; p=0.002).

Overall, patients with POEMS syndrome had nerve conduction slowing predominant in the nerve trunk, rather than in the distal nerve terminals, and axonal loss was prominent in the lower limb nerves. In contrast, CIDP patients showed conduction slowing in the distal nerve segments and multifocal conduction blocks. Representative waveforms of compound muscle action potentials in the median nerve of a patient with POEMS syndrome and in a patient with CIDP are shown in figure 1.

DISCUSSION

Our results show that approximately 50% of POEMS syndrome patients have neuropathy onset and 60% were misdiagnosed as suffering CIDP, resulting in a significant delay in diagnosis and consequently progression of the disease. Secondly, compared with CIDP, neuropathy in POEMS syndrome is characterised by

Table 2 Nerve conduction data for POEMS syndrome and CIDP patients

	A Normal (n=73)	B POEMS (n=51)	C CIDP (n=46)	p Value B vs C
Motor conduction study				
Median nerve				
Distal latency (ms)	3.6 (0.4)	5.6 (1.4)	8.1 (3.2)	<0.0001
CMAP amplitude (mV)	10.4 (2.9)	5.2 (3.8)	4.7 (3.3)	0.5
CMAP duration (ms)	4.8 (0.59)	6.6 (2.5)	8.5 (0.13)	0.13
Conduction velocity (m/s)	57.6 (3.7)	33.2 (10.0)	32.6 (11.2)	0.8
F wave latency (ms)	24.7 (1.8)	46.1 (13.6)	52.6 (13.9)	0.06
Terminal latency index	0.34 (0.03)	0.42 (0.11)	0.34 (0.16)	0.006
Conduction block		10% (5/50)	26% (11/43)	0.04
Not response	0% (0/73)	8% (4/50)	0% (0/43)	0.08
Tibial nerve				
Distal latency (ms)	4.3 (0.7)	7.2 (2.6)	8.3 (2.7)	0.1
CMAP amplitude (mV)	14.2 (4.7)	1.0 (2.3)	3.6 (3.5)	0.0001
Conduction velocity (m/s)	46.5 (3.8)	27.2 (6.6)	32.2 (7.5)	0.02
F wave latency (ms)	46.1 (3.8)	78.9 (15.4)	80.3 (19.6)	0.8
Not response	0% (0/73)	56% (27/48)	7% (3/42)	<0.0001
Tibial/median CMAP amplitude ratio	1.4 (0.5)	0.5 (0.8)	0.8 (0.6)	0.09
Sensory conduction study				
Median nerve				
SNAP amplitude (μV)	34.5 (14.8)	9.3 (9.7)	3.3 (6.0)	0.0005
Conduction velocity (m/s)	52.7 (8.3)	38.9 (7.0)	41.8 (9.1)	0.3
No response	0% (0/73)	22% (11/50)	63% (27/43)	<0.0001
Sural nerve				
SNAP amplitude (μV)	15.5 (7.8)	1.4 (2.4)	7.8 (8.8)	<0.0001
Conduction velocity (m/s)	51.4 (5.4)	37.4 (6.1)	43.6 (6.8)	0.004
No response	0% (0/73)	68% (32/47)	36% (15/42)	0.002
Sural/median SNAP amplitude ratio	0.5 (0.2)	0.3 (0.2)	3.2 (4.2)	0.02

Data are expressed as mean (SD) or per cent (number).
CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; POEMS syndrome, polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes syndrome; SNAP, sensory nerve action potential.

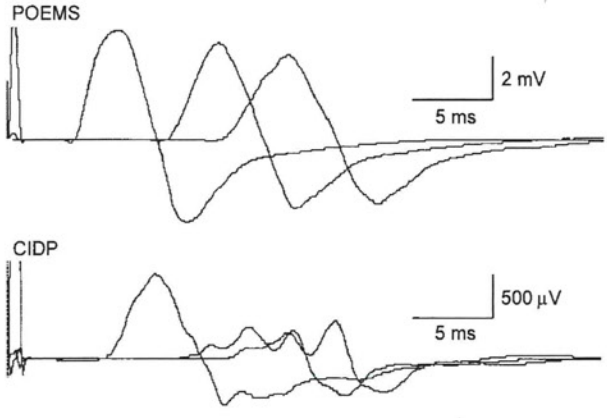

Figure 1 Findings in median motor nerve conduction studies in a patient with POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes) syndrome and in a patient with chronic inflammatory demyelinating polyneuropathy (CIDP). Compound muscle action potentials (CMAPs) were recorded from the abductor pollicis brevis after stimulation at the wrist, elbow and axilla. A 58-year-old man with POEMS syndrome showed normal distal latency (3.6 ms; normal <4.1 ms) but prominently slowed nerve conduction velocity (32 m/s; normal >48 m/s); demyelinative conduction slowing was dominant in the nerve trunk compared with the distal nerve terminals. In the CIDP patient (a 40-year-old woman), distal latency was prominently prolonged (6.3 ms) and distally evoked CMAP amplitude was markedly reduced (0.4 mV; normal >5.0 mV), suggestive of distal conduction block. Conduction block in the forearm segment (60% amplitude reduction) was also observed.

distal dominant painful polyneuropathy, particularly prominent neuropathic foot pain, being much more frequent than in CIDP. Finally, our findings confirm previous results[12 13]; different pattern of nerve conduction abnormalities between POEMS syndrome and CIDP, presumably reflecting the distinct pathophysiology of the two disorders.

Currently, POEMS syndrome is an under recognised disease, presumably because of the rarity of the disorder. A national survey conducted in Japan in 2003 showed a prevalence of approximately 0.3 per 100 000,[15] and the disorder was considered to be less prevalent in Western countries. The prevalence of CIDP has been reported to be similar in Europe and Japan, ranging from 1.9 to 3.6 per 100 000.[16–19] As mentioned above, POEMS syndrome has been increasingly recognised even in Western countries, and a series from the USA published in 2003 included 99 patients.[3] It is possible that POEMS syndrome is underestimated. As shown in the present study, a considerable number of patients with POEMS syndrome could be misdiagnosed or even undiagnosed. We suggest that POEMS syndrome should be considered as a differential diagnosis of demyelinating polyneuropathies.

This study also shows that neuropathic pain is a feature of POEMS syndrome. A histological study has reported that pain seen in patients with POEMS syndrome is closely related to a reduction in myelinated, but not unmyelinated, fibre population, suggesting that the painful symptoms in POEMS syndrome may be generated by well preserved unmyelinated C fibres due to lack of inhibitory myelinated A fibres.[20]

Previous electrophysiological studies have shown that patients with POEMS syndrome have: (1) slowing of nerve

conduction that was more predominant in the intermediate than in distal nerve segments; (2) rare conduction block; and (3) more severe attenuation of compound muscle action potentials in the lower than upper limbs.[12 13] In contrast, findings in CIDP patients were characterised by conduction slowing predominant in the distal nerve terminals, frequent conduction block in the nerve trunk and less discrepancy between upper and lower limb nerves.[12] Our results confirm these observations in a large number of patients. We suggest that, particularly in neuropathy onset POEMS patents without obvious systemic symptoms/signs, the specific patterns of nerve conduction abnormalities indicate the possibility of POEMS syndrome.

In immune mediated neuropathies such as typical CIDP, demyelination preferentially affects specific regions where the blood–nerve barrier is anatomically deficient, namely the distal nerve terminals and nerve roots.[21–23] In contrast, in POEMS neuropathy demyelination appears to predominantly involve the nerve trunk where the blood–nerve barrier functions. This is possibly mediated by VEGF induced diffuse breakdown of the blood–nerve barrier and this could result in homogenous rather than focally accentuated demyelination in CIDP.[4 23] The distribution of demyelinating lesions implies the pathophysiology of each disorder. POEMS syndrome could be distinguished from CIDP by clinical profile and patterns of nerve conduction abnormalities based on neuropathy features alone. If there are findings suggestive of the POEMS syndrome pattern, systemic and laboratory investigations should lead to the diagnosis. Recognition of these features contributes to early diagnosis and efficacious treatments in POEMS syndrome.

Contributors SN, SM and SK designed the study and wrote the manuscript. YS, KS, KK, YF, SO, SaM and ShK collected and analysed the data.

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Competing interests None.

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LETTER TO THE EDITOR

Factors associated with the efficiency of PBSC collection in POEMS syndrome patients undergoing autologous PBSC transplantation

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Polyneuropathy, organomegaly, endocrinopathy, M-protein, skin abnormalities (POEMS) syndrome is a rare plasma cell dyscrasia defined by the presence of peripheral neuropathy, monoclonal plasma cells and paraneoplastic features, such as skin changes and generalized edema.[1] Although the pathogenesis of this syndrome is unclear, it is believed to be related to excessive production of vascular endothelial growth factor (VEGF), probably secreted by clonal plasma cells or abnormally released by activated platelets.[2] Increased VEGF production appears to cause most disease features such as polyneuropathy, by inducing angiogenesis and microvascular hyperpermeability.

In the past decade, treatment of POEMS syndrome has expanded to include high-dose (HD) melphalan, followed by autologous PBSC transplantation (ASCT) and novel agents, including thalidomide, lenalidomide and bortezomib. Numerous reports have demonstrated that ASCT is the most effective therapy for these patients, causing improvement in multiple symptoms and VEGF levels.[3–7] However, collection of PBSCs in patients with POEMS syndrome is challenging, and such patients are at a higher risk than those with lymphoma or myeloma because of poor performance status (PS), morbidities associated with uncontrollable effusions or splenomegaly, and high serum VEGF levels. As the appropriate timing and factors associated with the efficiency of PBSC collection are unclear, we analyzed the factors affecting the efficiency of cell collection and engraftment in POEMS syndrome patients.

Subjects included 19 patients with POEMS syndrome, aged <65 years, without severe organ failure or active infection who underwent PBSC collection at Chiba University Hospital between December 2003 and November 2009. PBSC mobilization was performed either with 4 g/m^2 CY (HD-CY), followed by granulocyte G-CSF administration or G-CSF alone (5 μg/kg for 5 days). ASCT was performed with 200 mg/m^2 melphalan, with the dose reduced to 140 mg/m^2 in patients with PS 4. The effects of the harvest regimen, degree of splenomegaly, platelet count and VEGF levels on the efficacy of PBSC collection were evaluated. The number of 0.5 mm thick spleen slices obtained by CT was calculated to evaluate the spleen size.

Patient characteristics are shown in Table 1. Median age was 52 years (range; 34–64 years) and median time from onset of POEMS syndrome to PBSC collection was 14 months (range, 3–110 months). In all 12 patients received HD-CY and 9 received G-CSF alone for mobilization. The median number of total CD34+ cells was 4.56 × 10^6/kg (range, 0–9.60 × 10^6/kg), with the median number of cells in 100 mL of apheresis product in the HD-CY

Table 1. Patient characteristics and yield of PBSCs

No.	Age	Sex	M protein	Period from diagnosis to PBSC collection (mth)*	Prior therapy	Serum VEGF at diagnosis (pg/mL)	Pre PBSC collection				Harvest regimen	Number of aphereses	Total number of CD34+ cells (× 10^6/kg)	Number of CD34+ cells on the first day (× 10^6/kg/100 mL)
							Serum VEGF (pg/mL)	Slice No. of spleen	Plasma cells (%)	PLT (× 10^4/μL)				
1	41	F	IgA-λ	110	MP	>2000	>2000	18.2	6.2	16.3	HD-CY	1	4.50	2.65
2	41	M	IgG-λ	52	MP	>2000	ND	18	1.0	14.2	HD-CY	2	2.88	0.74
3	48	M	-	22	MP	>2000	ND	17	2.4	70.6	HD-CY	1	9.60	6.90
4	43	M	IgG-λ	12	None	7160	ND	16.8	1.4	4.6	HD-CY	2	5.99	1.87
5	58	F	IgG-λ	47	PSL	1920	1370	12.6	1.0	29.3	HD-CY	1	1.75	1.75
6	52	M	-	46	IVIG, PSL, IVMD	2840	1380	21	2.8	30.6	G-CSF	2	4.67	1.34
7	58	M	IgG-λ	8	None	2290	1560	24	2.4	ND	HD-CY	ND	-	-
8	53	M	IgA-λ	6	PSL	7880	2580	12.6	4.8	27.7	G-CSF	2	2.27	0.44
9	41	M	IgA-λ	12	Thal + DEX	5110	1010	21	2.6	13.1	G-CSF	2	2.2	0.1
							751	21	0.6	12.4	HD-CY	2		0.17
							ND	18	ND	12.1	G-CSF	2		0.32
10	49	M	IgA-λ	32	VAD, EDX, MPAnti-VEGF Ab, Thal	4480	4480	22	1.4	66.4	G-CSF	2	2.29	0.73
11	51	M	IgG-λ	17	PSL, Thal + DEXCHOP	2130	759	16.8	0.4	5.7	HD-CY	1	4.47	2.47
12	61	M	IgG-λ	4	None	1340	1340	16	3	14.5	HD-CY	1	4.68	2.45
13	58	M	IgA-λ	13	Thal + DEX	2950	2950	16.8	1.2	7.4	HD-CY	1	4.64	2.56
14	34	F	IgG-λ	3	IVIG, PSL, Thal	3990	ND	17.6	3.6	23.8	HD-CY	1	8.74	5.05
15	62	M	IgG-λ	9	DEX	8160	8160	12.6	2.8	3.5	HD-CY	1	5.12	2.47
16	57	M	IgA-λ	14	IVIG, Thal + DEX	4810	ND	16	2	29.1	G-CSF	2	4.32	1.28
17	64	F	IgA-λ	32	PSL, Thal + DEXAnti-VEGF Ab	23 000	25	16	0.3	36.1	G-CSF	2	5.2	1.53
18	47	F	IgA-λ	16	Thal + DEX	9950	1340	15	6	22.8	G-CSF	1	5.0	2.1
19	64	F	IgG-λ	48	MP, Thal	2540	883	22	3.2	24.1	G-CSF	1	0.29	0.16
Median	52			16		2950	1370	17	2.4	19.4			4.56	1.44

Abbreviations: DEX = dexamethasone; HD-CY = high-dose cyclophosphamide; IVIG = intravenous immunoglobulin; IVMD = intravenous melphalan and dexamethasone; MP = melphalan and prednisolone; ND = not done; PSL = prednisolone; Thal = thalidomide; VAD = vincristine, doxorubicin and dexamethasone; VEGF = vascular endothelial growth factor. *The period from onset of the disease to PBSC collection.

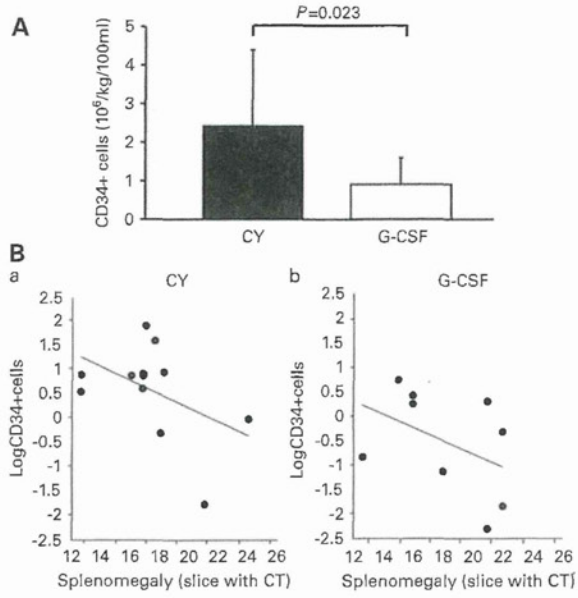

Figure 1. PBSC collection in POEMS syndrome. (**A**) Correlation analysis of CD34+ cells/BW (kg)/100 mL of apheresis products collected on the first day between the HD-CY and G-CSF groups. We collected a significantly higher number of CD34+ cells in the HD-CY group than in the G-CSF group ($P=0.023$) as determined by Student's *t*-test. (**B**) Correlation between CD34+ cells/BW (kg)/100 mL of apheresis products collected on the first day and splenomegaly. (a) HD-CY group, (b) G-CSF group. Regression analysis demonstrated that splenomegaly was associated with a decrease in the efficacy of PBSC collection in the HD-CY ($r=-0.435$) and G-CSF ($r=-0.435$) groups.

group significantly higher than that in the G-CSF group (2.45×10^6/kg (range; 0–6.9×10^6/kg) vs 0.73×10^6/kg (range, 0.1–2.1×10^6/kg), $P=0.023$; Figure 1A). However, the proportion of patients with $>2\times10^6$ cells/kg was not significantly different between the two groups ($P=0.203$).

We examined the relationship between the efficiency of PBSC collection, and serum VEGF levels and platelet counts. Median serum VEGF level and platelet counts before PBSC collection were 1370 pg/mL (range; 25–8160 pg/mL, $n=13$) and $19.4\times10^4/\mu$L (range; 4.6–$66.4\times10^4/\mu$L), respectively. There was no correlation between VEGF levels or platelet counts and efficacy of PBSC collection. Conversely, splenomegaly was associated with a decrease in the efficacy of PBSC collection in the HD-CY ($r=-0.462$) and G-CSF ($r=-0.435$) groups (Figure 1B). We could not harvest sufficient PBSCs in two patients (no. 7 and 19) with severe splenomegaly (24 and 22 slices, respectively).

A total of 17 patients underwent ASCT with a median infused CD34+ cell dose of 2.3×10^6/kg (range, 1.4–4.8×10^6/kg), and all patients were engrafted. The median time of neutrophil, platelet, and reticulocyte engraftment was 13 (range, 9–17 days), 13.5 (range, 8–31days) and 17 days (range, 13–36 days), respectively. The time of engraftment did not differ between the HD-CY ($n=10$) and G-CSF ($n=6$) groups. Three patients (17.6%) developed engraftment syndrome requiring steroid treatment and one (no. 15) required mechanical ventilation and hemodialysis.

Splenomegaly was associated with a decrease in the efficacy of PBSC collection in the HD-CY and G-CSF groups. We failed to collect stem cells in 2 patients with severe splenomegaly, although patient no. 9 yielded sufficient PBSCs after improvement in splenomegaly by thalidomide + dexamethasone. These results suggest that controlling disease status is important to collect sufficient PBSCs. As melpharan is potentially deleterious to stem cells, it should not be used as the initial treatment before PBSC harvest, with thalidomide or lenalidomide combined with dexamethasone being the treatment of choice to control pleural effusion, ascites and serum VEGF levels.

Serum VEGF levels at the time of PBSC collection did not influence the efficiency of collection. This suggests that VEGF level is not a factor for predicting the optimal timing of PBSC collection. Although a correlation between disease course and VEGF levels has been reported,[8] Goto *et al.*[9] showed a discrepancy between disease activity and VEGF levels in POEMS syndrome patients. Because of the relatively small number of patients in our study, further evaluation is required to determine whether a relationship exists between the efficiency of PBSC collection and VEGF levels.

In the present study, PBSCs were collected using either HD-CY with G-CSF or G-CSF alone. We were able to collect a significantly higher number of CD34+ cells in the HD-CY group than in the G-CSF group. However, there was no significant difference between the two groups in the number of patients who yielded $>1\times10^6$/kg of PBSCs in 100 mL of apheresis product on the first day of collection. This is considered a sufficient number for a single ASCT.

In summary, we evaluated factors associated with the efficacy of stem cell collection in patients with POEMS syndrome. Splenomegaly may be a predictive factor for poor mobilization. G-CSF monotherapy is a suitable regimen for safe and efficient PBSC collection. Suitable prior therapy should be performed in patients considered poor mobilizers in order to establish a treatment strategy that includes optimal timing for effective and safe PBSC collection leading to a successful outcome in ASCT.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Treatment for POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome (Review)

Kuwabara S, Dispenzieri A, Arimura K, Misawa S, Nakaseko C

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[Intervention Review]

Treatment for POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome

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ABSTRACT

Background

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare cause of demyelinating and axonal mixed neuropathy with monoclonal plasma cell proliferative disorder and multiorgan involvement. The pathogenesis of POEMS syndrome is not well understood, but overproduction of vascular endothelial growth factor (VEGF), probably secreted by plasmacytomas, is likely to be responsible for most of the characteristic symptoms. POEMS syndrome is a potentially fatal disease, and patients' quality of life deteriorates because of progressive neuropathy, massive pleural effusion or ascites, or thromboembolic events. There is a need for efficacious therapy to improve prognosis. This is the first update of a review first published in 2008.

Objectives

To assess the effects of treatment for POEMS syndrome.

Search methods

We searched the Cochrane Neuromuscular Disease Group Specialized Register (23 February 2012), CENTRAL (2012, Issue 2), MEDLINE (January 1966 to February 2012), EMBASE (January 1980 to February 2012) and CINAHL Plus (January 1937 to February 2012) for all papers on POEMS syndrome

Selection criteria

We sought all randomized and quasi-randomized controlled trials, and non-randomized controlled studies. Since we discovered no such clinical trials, we assessed and summarized all retrospective case series including five or more patients in the 'Discussion' section.

Data collection and analysis

Two review authors independently reviewed and extracted details of all potentially relevant trials with any treatment for POEMS syndrome. We then collated and summarized information on the outcome.

Main results

We found no randomized or non-randomized prospective controlled trials of treatment for POEMS syndrome. We summarized the results of retrospective case series containing five or more patients in the 'Discussion' section.

Authors' conclusions

There are no randomized or quasi-randomized controlled clinical trials of treatment for POEMS syndrome on which to base practice.

PLAIN LANGUAGE SUMMARY

Treatment for POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes)

POEMS syndrome is a rare disorder of the blood which can cause a polyneuropathy (nerve symptoms such as numbness, tingling, pain, and muscle weakness) but can also involve many of the organs of the body, causing enlarged organs or organomegaly (usually liver, spleen, and lymph nodes), changes in hormone production or endocrinopathy (gynecomastia in men), abnormal blood protein (M-protein), and skin changes such as increased pigmentation or skin thickening. Its cause is not known. The quality of life of people with POEMS deteriorates because of progressive neuropathy, and accumulation of fluid in the limbs or in the abdominal cavity or cavity around the lungs. It is a potentially fatal disease, and serious complications can arise due to multiorgan failure. There is no established treatment regimen, but potentially effective treatments that have been tried include chemotherapy, irradiation, corticosteroids, thalidomide or lenalidomide, and blood stem cell transplantation. This review found no randomized controlled trials of treatments for POEMS syndrome. Prospective treatment trials are needed to establish the relative values of different treatments.

BACKGROUND

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare cause of demyelinating and axonal mixed neuropathy with monoclonal plasma cell proliferation and multiorgan involvement (Bardwick 1980; Nakanishi 1984). Skin changes include angiomata, skin thickening, pigmentation, and hypertrichosis. Important clinical features other than the five cardinal symptoms of POEMS include peripheral edema, pleural effusion, ascites, sclerotic bone lesions, Castleman disease, papilledema, polycythemia, and thrombocytosis. POEMS syndrome has also been called Crow-Fukase syndrome, Takatsuki syndrome, and PEP (plasma cell dyscrasia, edema, and pigmentation) syndrome. The prevalence of POEMS syndrome is unclear, but a recent national survey conducted in Japan showed a prevalence of approximately 0.3 per 100,000 (Arimura 2007). The disease was initially thought to be more common in Japan given that the largest initial reports were from Japan (Takatsuki 1983; Nakanishi 1984). However, large series have also been reported from France (Soubrier 1994), the United States (Dispenzieri 2003; Allam 2008), China (Cui 2011; Li 2011b), and India (Kulkarni 2011), and the disorder has been increasingly recognized in many areas of the world.

The neuropathy is a symmetric sensory-motor polyneuropathy, predominantly affecting the distal lower limbs. Neuropathologically, a mixture of demyelination and axonal degeneration is usually present. Uncompacted myelin lamellae are found in most cases, and have been suggested to be highly characteristic of this syndrome (Vital 2003). Segmental demyelination, particularly in the proximal nerve segments, endoneurial edema, and involvement of endoneurial vessels are also frequently seen (Koike 2000; Scarlato 2005). POEMS syndrome is frequently mistaken for chronic inflammatory demyelinating polyneuropathy (CIDP) because both disorders show peripheral nerve demyelination (Sung 2002; Mauermann 2012; Nasu 2012). It is necessary to recognize POEMS syndrome as a cause of demyelinating neuropathy, and the differentiation from CIDP is clinically very important because fundamentally different treatments are required for each disease (Dispenzieri 2011; Kuwabara 2011).

POEMS syndrome is a potentially fatal disease, and patients' quality of life deteriorates because of progressive neuropathy (Isose 2011), massive peripheral edema, pleural effusion, or ascites. Serious complications such as multiorgan failure from capillary leak syndrome, restrictive lung disease, pulmonary hypertension (Allam 2008), and thromboembolic events may occur, contributing to the poor prognosis. In a retrospective series involving 102 Japanese patients in the 1980s, most of whom were treated with corticosteroids without chemotherapy, follow-up data were avail-

able in 58 patients. Thirty-eight of them died, with a mean survival period of 33 months (Nakanishi 1984). In another retrospective study conducted in the United States, more intensive treatments were administered; out of 99 patients, 65 were treated with irradiation to a local osteosclerotic lesion and 48 with melphalan and prednisone. Overall median survival was 165 months, but patients with edema, effusion, or ascites had a mean survival of 79 months, and patients with fingernail clubbing had a mean survival of 31 months (Dispenzieri 2003). In a report from Italy, 6 of 11 patients died 3 to 23 months after combined treatment with corticosteroids, alkylating agents, and/or plasma exchange (Scarlato 2005). In one French study, at least 7 out of 15 patients were alive for more than five years (Soubrier 1994).

The pathogenesis of POEMS syndrome is not well understood, but overproduction of vascular endothelial growth factor (VEGF), probably secreted by plasmacytomas (Nakajima 2007), is likely to be responsible for most of the characteristic symptoms (Watanabe 1996; Soubrier 1999). Almost all patients with POEMS syndrome have highly elevated serum VEGF levels, and disease activity appears to correlate with VEGF levels (Watanabe 1998; Hashiguchi 2000; D'Souza 2011). VEGF is a potent multifunctional cytokine that induces prominent angiogenesis and microvascular hyperpermeability, and therefore could cause many of the symptoms of POEMS syndrome.

There are no randomized controlled trials (RCTs) for POEMS syndrome, presumably because of the rarity of the disorder, and therefore no established treatment regimen. Previous case reports and series have described patients with POEMS syndrome who have been treated with irradiation, resection of plasmacytomas, chemotherapies, corticosteroids, plasmapheresis, and intravenous immunoglobulin infusion. Irradiation has usually been proposed for patients with a solitary plasmacytoma. If patients have wide spread osteosclerotic lesions, systemic chemotherapy is necessary (Kuwabara 1997; Dispenzieri 2005a; Dispenzieri 2005b). In appropriate candidates, high-dose chemotherapy with autologous peripheral blood stem cell transplantation (auto-PBSCT) is recommended (Jaccard 2002; Dispenzieri 2004; Kuwabara 2006). This treatment resulted in obvious improvement in neuropathy as well as other symptoms, with a significant decrease in serum VEGF levels (Kuwabara 2008a; D'Souza 2011). From data of published experience, the transplant-related mortality was initially reported to be 7.4% (Dispenzieri 2005a), but an update in 2008 suggested a lower transplant-related mortality (3.3%) with better peri-transplant supportive care (Dispenzieri 2008). Indications for this treatment have not yet been established, and long-term prognosis is unclear. Treatments that may be considered in the future include lenalidomide or thalidomide, anti-VEGF monoclonal antibody (bevacizumab), and bortezomib.

No RCTs for POEMS syndrome had been published when the protocol for this review was written in 2008 or at the time of this update in 2012. This review attempts to systematically consider the available evidence and highlights the need for clinical trials and prospective data collection in POEMS syndrome. It should serve as a basis for maintaining an up-to-date record.

OBJECTIVES

To assess the effects of treatment for POEMS syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for all RCTs or quasi-RCTs (alternate or other systematic treatment allocation). It was anticipated that this type of evidence would not be available, and therefore we also sought non-randomized trials. We planned to report historically controlled trials and trials with concurrent controls, provided adequate diagnostic criteria were applied, and adequate descriptions of interventions and clinical courses were stated.

Given the anticipated lack of studies that included pre-planned data collection and eligibility criteria, and in an attempt to summarize the available clinical data, we have reviewed other types of studies and summarized them in the Discussion. We have included comparative cohort studies, case-control studies and case series of at least five participants in this assessment.

Types of participants

Eligible studies had to include participants of any age with POEMS syndrome. The clinical manifestations should not be explained by other neurological or haematological disease, including neuropathy associated with systemic vasculitis, neuropathy associated with anti-MAG (myelin-associated glycoprotein) antibody, and multiple myeloma. Appropriate clinical and laboratory investigations should have been performed to exclude other recognized causes of the neuropathy (Dispenzieri 2005a; Dispenzieri 2011).

It is recognized that not all five features of 'POEMS' are required to make the diagnosis of POEMS syndrome (Dispenzieri 2003), and that an elevated serum VEGF level is a diagnostic marker (Watanabe 1996). However, measurements of serum VEGF were not widely available until 2000, and many earlier reports were missing this information. This review will include patients as having definite or probable POEMS syndrome using the following diagnostic criteria modified from Dispenzieri 2005a and Dispenzieri 2007a.

Criteria for the diagnosis of POEMS syndrome

Major criteria

(a) Polyneuropathy (mandatory)
(b) Monoclonal plasma cell proliferative disorder (mandatory)*
(c) Elevation of serum or plasma VEGF levels
(d) Sclerotic bone lesions
(e) Castleman disease**

Minor criteria

(f) Organomegaly (hepatosplenomegaly or lymphadenopathy)
(g) Edema (edema, pleural effusion, or ascites)
(h) Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, or pancreatic)***
(i) Skin changes (hyperpigmentation, hypertrichosis, plethora, cyanosis, hemangiomata, or white nails)
(j) Papilledema
(k)Thrombocytosis and/or polycythemia
(1) Definite POEMS syndrome: three major criteria and at least one minor criterion.
(2) Probable POEMS syndrome: two major criteria, with at least one minor criterion.
* Defined by M-protein, or monoclonal plasma cell proliferation in bone marrow biopsy or biopsy of a plasmacytoma or sclerotic lesion.
** There is a Castleman disease variant of POEMS syndrome that occurs without evidence of a clonal plasma cell disorder that is not accounted for in this list. This entity should be considered separately.
***Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.

Types of interventions

We considered all interventions. We had anticipated that most studies would focus on the use of focal irradiation, corticosteroids, alkylating agent-based chemotherapy, high-dose chemotherapy with auto-PBSCT, lenalidomide or thalidomide, bevacizumab (anti-VEGF monoclonal antibody), bortezomib, or combinations of these treatments. We considered studies that have compared one treatment with another or against placebo. We have also assessed series that have reported outcomes in patients not receiving any of the above treatments in the Discussion.

Types of outcome measures

Primary outcomes

Survival two years after initiation of treatment.

Secondary outcomes

The secondary outcome measures include improvement in disability as defined by the original authors at least one year after the start of treatment. Where possible, we planned to transform disability data to the Overall Neuropathy Limitations Scale (ONLS) (Graham 2006). We defined improvement as at least one grade decrease on this scale. We considered unchanged or increased grades on the scale as no improvement:

Arm grade

"0 = Normal" to "5 = Disability in both arms preventing all purposeful movement".

Leg grade

"0 = Normal" to "7 = Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs".

Assessment of manifestations of disease was also evaluated one year after the start of treatment.

1. Improvement by one or more ONLS grades.
2. Disappearance of extravascular volume overload (edema, pleural effusion, and ascites).
3. Normalization of serum VEGF levels.
4. Disappearance of M-protein.
5. Adverse effects attributable to treatment, which require or prolong hospitalization, including treatment-related death.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Neuromuscular Disease Group Specialized Register (23 February 2012) using the following search terms: "POEMS syndrome", its synonyms "Crow-Fukase syndrome", "Takatsuki syndrome", and "PEP (plasma cell dyscrasia, edema, and pigmentation) syndrome", and "paraproteinemia". We adapted this strategy to search for all papers on POEMS syndrome in CENTRAL (2012, Issue 2), MEDLINE (January 1966 to February 2012), EMBASE (January 1980 to February 2012) and CINAHL Plus (January 1937 to February 2012). The detailed search strategies are in the appendices: Appendix 1 (MEDLINE), Appendix 2 (EMBASE), Appendix 3 (CINAHL Plus) and Appendix 4 (CENTRAL).

Searching other resources

We reviewed the bibliographies of the trials and studies identified, contacted the authors and known experts in the field, and approached pharmaceutical companies to identify additional published or unpublished data