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ORIGINAL ARTICLE

Clinical characteristics and the long-term outcome of patients with atypical POEMS syndrome variant with undetectable monoclonal gammopathy

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Abstract

The diagnosis of polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome requires polyneuropathy and monoclonal plasma cell proliferation as two mandatory criteria. Our aim was to summarize clinical manifestations and treatment responses of POEMS variants with no evidence of monoclonal gammopathy. We queried all medical documentation of patients referred to Peking Union Medical College Hospital from August 2012 to July 2017, and reviewed the clinical and laboratory features of 13 patients with atypical POEMS syndrome with undetectable monoclonal gammopathy, and compared to prototypes published. The prevalence of polyneuropathy, organomegaly, skin changes, and extravascular fluid overload were 100%, 100%, 92%, and 100%, respectively. Other clinical manifestations, such as endocrinopathy, pulmonary hypertension, papilledema, thrombocytosis, and polycythemia affected similar percentages of patients as seen in prototypes. POEMS variants enrolled had a median serum vascular endothelial growth factor (VEGF) level of 4998 pg/ml (range 2155–11,029 pg/ml). Long-term follow-up found that all 12 patients received autologous stem cell transplant, melphalan-based therapy or lenalidomide/thalidomide-based therapy obtained clinical improvement, of which eight experienced decreased levels of VEGF by 50% or back to normal. The median progression-free survival was 101.5 months. Our findings raised a variant of POEMS syndrome variants with featured clinical manifestations, elevated VEGF levels, and good response to therapies targeting plasma cell.

Keywords POEMS syndrome · Vascular endothelial growth factor · Monoclonal gammopathy · Plasma cell

Introduction

POEMS syndrome is rare plasma cell neoplasm named after its featured paraneoplastic constellations of polyneuropathy, organomegaly, endocrinopathy, monoclonal protein (M protein), and skin changes, and several other common clinical presentations including thrombocytosis, erythrocytosis, sclerotic bone lesions, Castleman disease (CD), papilledema, extravascular fluid overload (peripheral edema, ascites, pleural effusions), fatigue, and clubbing [1]. The diagnosis of POEMS is based on a composition of clinical and laboratory features. According to the criteria updated in 2017, the diagnosis of POEMS requires polyradiculoneuropathy and monoclonal plasma proliferating as two mandatory criteria, at least one of the major criteria (CD, elevated vascular endothelial growth factor (VEGF) level, and sclerotic bone lesion), and at least one of the minor criteria (organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, thrombocytosis/polycythemia) [2].

Elevated levels of VEGF is a hallmark of POEMS syndrome. Studies have shown that plasma VEGF levels over 200 pg/mL has a specificity of 95% and a sensitivity of 68% in support of a diagnosis of POEMS syndrome [3]. Prior studies based on newly diagnosed patients with POEMS syndrome referred to our institute have shown a median level of serum VEGF of 3503 ng/L (range, 111–13,867 ng/L), markedly elevated in comparison to other plasma cell neoplasm or health controls, and a cutoff value of 1200 ng/L has a specificity of 90.2% and a sensitivity of 83.7% [4]. In addition, several studies failed to reach consensus on the prognostic value of VEGF level. A recent study by Zhao et al. conducted

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within a large cohort of 476 patients confirmed that VEGF response was strongly associated with hematological response in consideration of progression-free survival and overall survival rates and could serve as a potential surrogate end point in clinical researches [5].

This multisystem disorder is of high heterogeneity, and few variants of POEMS with no evidence of monoclonal gammopathy have been described, which further complicated the diagnosis in clinical practice [6–9]; however, previous reported variants of POEMS were limited by sample size, with no long-term outcome available.

We summarized clinical manifestations and long-term outcomes of 13 patients suspected of a variant form of POEMS syndrome with undetectable M protein. The diagnosis was made by comprehensive consideration of characteristic clinical and laboratory features, together with high level of serum VEGF. Moreover, we further evaluated the value of serum VEGF in the diagnosing of POEMS syndrome.

Subjects and methods

Study subjects

We queried all medical documentation of patients referred to Peking Union Medical College Hospital from August 2012 to July 2017 to identify all patients suspected of POEMS syndrome. Patients recruited in our study were those who had polyneuropathy but no detectable M protein. All patients signed informed consent, and the study was approved by the Institutional Review Board of Peking Union Medical College Hospital, in accordance with the Declaration of Helsinki.

Definition and evaluation

Clinical manifestations and lab tests were carefully reviewed at baseline. The absence of M protein was confirmed by negative serum and urine protein electrophoresis (sPEP) and immunofixation electrophoresis (sIFE), and normal serum immunoglobulin free light chains ratios (sFLCR). The serum FLC assay (Freelite, Binding Site, Birmingham, UK) was performed on a Bade Behring BN II Nephelometer with the following ranges: κ, 3.3–19.4 mg/L, and λ, 5.7–26.3 mg/L. Additionally, the absence of monoclonal plasma cell expansion was confirmed by negative immunohistochemistry studies in bone marrow aspiration or biopsy. Polyneuropathy was depicted by both sensation and motoring dysfunctions, and a standard ONLS scoring system was applied [10]. Serum VEGF levels were tested at baseline using a Human VEGF Quantikine ELISA Kit (R&D Systems, Minneapolis, MN, USA). β-Isomerized C-telopeptide (β-CTX) was measured using an automatic analyzer (Roche Cobas E601; Holliston, MA, USA) with Elecsys reagent kits (Roche Diagnostics, Basel, Switzerland). Other laboratory tests including serum creatinine, platelet counts, hemoglobin levels, and endocrinological tests were also evaluated at baseline. X rays were ordered to evaluate bone lesions. Results of fundus examination and echocardiography were also reviewed.

Subsequent follow-up visits were scheduled every 3 to 6 months. Upon follow-up, both of serum VEGF level and β-CTX level were used to monitor disease activity, and tests for M protein (sPEP, sIFE, and sFLC) were repeated [11].

Treatment response

In consideration of the M protein being immeasurable and the infeasibility of bone marrow biopsy, clinical responses were evaluated based on objective improvements in any of the symptoms of POEMS syndrome, that is, alleviation of peripheral neuropathy, or attenuation of fluid overload. Clinical responses were noted as I_C and NI_C, for clinically improved and clinically not improved, respectively. VEGF response was defined as CR_V (normalized VEGF), PR_V (VEGF improved by at least 50%), and NR_V (not meeting either CR_V or PR_V) [5, 12].

Similarly, disease progression and relapse were defined based on clinical evaluation and VEGF levels: persistence, exacerbation, or newly onset of symptoms attribute to POEMS syndrome, together with increased VEGF level by 50% of in comparison with the latest VEGF level.

As patients of typical POEMS syndrome can derive very significant clinical benefits in the absence of M-protein response, the emergence of M protein detectable by sPEP, sIFE, or sFLC was noted and recorded in our study [13, 14]; however, such tests provide limited value in monitoring response to treatment and thus were not considered as M-protein response.

Survival analyses and statistical analyses

As no deaths were observed in our cohort, progression-free survival (PFS) was defined as the time from diagnosis to the time of progression or relapse and calculated using Kaplan-Meier method. Data analysis was conducted using R (version 3.4.3). Fisher's exact test and the Chi-square test were applied to comparing clinical characteristics of recruited POEMS variants and POEMS prototypes published before. A P value less than 0.05 was considered to be statistically significant.

Results

Baseline characteristics

Thirteen patients (six men and seven women) who met the inclusion criteria were identified from August 2012 to July 2017 by manual search. Clinical and laboratory features of enrolled patients at diagnosis were summarized in Table 1.

Table 1 Baseline characteristics and clinical manifestation of enrolled patients

	Basic information			Mandatory major criteria			Other major criteria			Minor criteria					
	Age at onset	Age at diag.	Sex	Polyneuropathy (ONLS score)	Monoclonal plasma cell-proliferative disorder	Plasma cell (% in BM smear), BM biopsy	Castle-man disease	Bone lesions	VEGF (pg/ml)	Organomegaly (LN, hepatomegaly, splenomegaly)	Extravascular overload (Edema, ascites, pleural effusion, pericardial effusion)	Endocrinopathy (Adrenal[1], thyroid[2], prolactin[3], gonadal[4], DM)	Skin[5]	Papill-edema	Plt (/ul), Hb (g/L)
1	40	41	M	7	N	N	\	N	6617	Y, N, N	N, N, Y, N	N, N, Y, Y, Y	Y	0	201, 177
2	57	58	M	4	N	N, N	\	Lytic	3467	N, Y, Y	Y, N, N, Y	N, N, Y, Y, Y	Y	1	273, 152
3	44	45	M	5	N	0.5, N	N	Lytic	2581	Y, Y, N	Y, Y, Y, Y	Y, Y, Y, Y, N	Y	1	277, 134
4	38	44	F	4	N	1.5, N	\	N	5375	Y, Y, Y	Y, Y, Y, Y	Y, N, N, \, N	Y	1	386, 95
5	44	45	F	5	N	N, N	Y	Sclerotic	6331	Y, N, Y	Y, N, Y, N	N, Y, Y, \, N	Y	0	732, 121
6	25	26	F	5	N	N	\	Sclerotic	5525	N, N, Y	N, N, N, Y	Y, Y, N, \, N	Y	1	170, 161
7	56	57	F	4	N	N, focal PC	\	Sclerotic	6050	Y, N, Y	Y, Y, N, Y	Y, Y, \, \, N	N	0	504, 163
8	47	47	F	9	N	3.0, focal PC	\	Sclerotic	2155	Y, N, Y	N, N, N, N	\, N, N, \, Y	Y	1	582, 138
9	40	51	M	2	N	N	\	Mixed	3478	Y, Y, Y	Y, N, Y, Y	Y, N, Y, Y, N	Y	1	295, 159
10	49	53	M	9	N	N	\	N	3725	Y, N, N	Y, N, N, N	N, Y, Y, N, N	Y	0	348, 123
11	46	49	M	1	N	N	Y	N	11,029	Y, Y, Y	Y, Y, N, Y	Y, Y, Y, Y, Y	Y	1	426, 112
12	51	55	F	10	N	3.5, scattered PC	Y	Sclerotic	3217	Y, Y, Y	Y, Y, Y, Y	Y, Y, Y, \, N	Y	1	123, 66
13	40	42	F	1	N	2.5, N	\	Sclerotic	4998	Y, N, Y	Y, Y, Y, Y	N, Y, N, \, N	Y	0	346, 124

Abbreviations: *Y* symptom exist or positive results, *N* symptom not exist or negative results, *NA* not available or not evaluable, *PC* plasma cell in bone marrow biopsy, *BM* bone marrow, *VEGF* vascular endothelial growth factor, *LN* lymph node enlargement, *DM* diabetes mellitus, *Plt* platelet count, *Hb* hemoglobin

[1] Adrenal insufficiency, defined as ACTH (adrenocorticotropic hormone) higher than upper limit of normal range 46 pg/ml in our institute

[2] Hypothyroidism, documented in patients' medical records or evaluated at admission by elevated TSH (thyroid stimulating hormone) over normal range (0.28~4.34 uI U/ml)

[3] Hyperprolactinemia, defined as serum prolactin level hither than 13.13 ng/ml for male and 30 ng/ml for female patients

[4] Gonadal disorders include impotence or gynaecomastia, and were only evaluated for male patients

[5] Skin changes represent any kind of hyperpigmentation, hypertrichosis, skin hemangiomata, skin thickening, and/or white nails

The median onset age was 44 years (range, 25–57 years), while the median age of diagnosis was 47 years old (range, 26–58). The most common initial symptoms were numbness and/or weakness of limbs due to peripheral neuropathy (nine in thirteen enrolled patients). Eight of the enrolled patients have been misdiagnosed and treated with glucosteroids, one with intravenous immunoglobulin.

Neuropathy

All patients had neuropathy affecting both motor and sensory functions confirmed by electromyography. The mean ONLS score was 2 (range, 0–4) for upper limbs and 3 (range 0–6) for lower limbs. Two enrolled patients received sural nerve biopsy, one with axonal lesion, and the other with mixed axonal loss and demyelination.

Of 11 patients who underwent lumbar puncture, seven patients had elevated cerebrospinal fluid opening pressure over 180 mmH_2O, and the overall median level of open pressure was 200 mmH_2O (range, 150–310 mmH_2O). The cerebral fluid protein levels were beyond normal range for all 11 patients, with a median level of 1.77 g/L (range, 0.97–2.42 g).

Organomegaly

All 13 enrolled patients had organomegaly, including hepatomegaly ($n = 6$), splenomegaly ($n = 10$), and enlarged lymph node ($n = 11$). Among four patients who underwent lymph node biopsy, three patients were confirmed of Castleman disease of the hyaline-vascular type, and the remaining patient had reactive hyperplasia of the lymph node.

Endocrinopathy

Among eight patients with hypothyroidism, six had subclinical hypothyroidism with elevated thyroid-stimulating hormone (TSH) only at diagnosis, two of which received hormone replacement therapy. All six male patients had elevated prolactin levels (range 13.95–445.8 ng/ml, normal 2.64–13.13 ng/ml) and estrogen levels (range 48.75–78 pmol/L, normal < 47 pmol/L). Two male patients had decreased testosterone levels. Five patients complained of impotence, and two of gynecomastia.

Skin changes

Skin changes were noted in 12 of 13 patients enrolled, with local/general hyperpigmentation was the most common change, followed by skin hemangiomata.

Extravascular volume overload

Peripheral edema, ascites, pleural effusion, and pericardial effusion were noted in ten, six, seven, and nine patients, respectively. Four patients suffered from all four kinds of extravascular overload simultaneously.

Bone lesion

X-rays of the skull, vertebrae, pelvis, femur, and humerus, and CT scans from thorax to abdomen were performed as routine screening for bone lesions. Nine patients had bone lesions, of which six had sclerotic bone lesions, two had lytic lesions, and one had mix sclerotic and lytic lesions.

β-CTX was tested for 12 patients as a serum marker for bone remodeling. All 12 patients tested had elevated bCTX level ranging from 0.707 to 3.4 ng/ml with a median value of 1.35 ng/ml (normal 0.26–0.512 ng/ml).

Bone marrow examination

Bone marrow (BM) aspiration and biopsy were performed for enrolled patients, of which eight were unremarkable. Three patients had plasma cell counts in bone marrow smears over 2% (range 2.5–3.5%), and three patients had focal or scattered plasma cell proliferation seen in BM biopsy. Immunohistochemistry staining of BM was done in all patients, with no evidence of monoclonal plasma cell expansion. One patient had CT-guided bone lesion biopsy of the lumber vertebrae, and was found with scattered plasma cells with no light-chain restriction.

Serum VEGF levels

All enrolled patients were tested for serum VEGF at recruiting. The median level of serum VEGF was 4998 pg/ml, ranging from 2155 to 11,029 pg/ml.

Other manifestations

Eight of enrolled patients had papilledema confirmed by fundus examination. Two of nine patients having transthoracic Dopplar echocardiography were diagnosed with pulmonary hypertension with an estimated pulmonary artery systolic pressure over 50 mmHg. Two of four patients with pulmonary function tests had restrictive lung disease.

Response to treatment

Six patients received autologous stem cell transplants, of which three were treated with lenalidomide before transplant. One received radiotherapy plus glucocorticoid. Four received novel agent-based therapy, that is, three with lenalidomide-

based and one with thalidomide-based regimen. Only one patient was treated with melphalan-based therapy. The remaining one was treated simply for symptom relief.

All 12 patients treated obtained clinical improvement. Defined as reduction of ONLS score of at least one unit, neurological response was seen in nine patients. The mean ONLS scores declined from 5.08 to 2.54, and two patients recovered completely. The initial responses were seen in four patients at the first 3 months of treatment, and three more patients till sixth month. Nearly all patients improved in organomegaly and extravascular overload as treatment processed. Two relapses were noticed. The patient receiving only symptom control medication had no improvement. Table 2 shows the change in clinical symptoms and VEGF level of all recruited patients.

VEGF responses were plotted by time-from-treatment in Fig. 1. Ten patients had follow-up VEGF data, of which three CRv, five PRv, and two NRv were observed. The median time to CRv/PRv was 8.3 months (range, 2.8–28.1 months). Three patients of CRv/PRv had VEGF-relapse, and the time from initiation of treatment to VEGF-relapse was 21.0, 39.8, and 12.2 months, respectively. The time of VEGF-relapse prior to clinical relapse was about half a year (5.6 months) in one patient. The other two patients with VEGF-relapse had no clinical relapse observed for 44.7 months and 8.5 months till the latest follow-up, respectively.

Long-term monitoring of M-protein also identified the emergence of M protein by sIFE in two enrolled patients 7.5 and 22.9 months after diagnosis; however, these two patients with M-protein emergence had no evidence of clinical or VEGF-relapse.

Survival analysis

The median follow-up was 25 months with a range of 7 to 126 months. Kaplan-Meier estimate of survival rate was estimated and the median progression-free survival considering clinical and VEGF relapse was 101.5 months (95% CI 39.8~NA months).

Compare to prototype of POEMS

We summarized clinical and laboratory features of a series of 13 POEMS variants with undetectable M protein, and compared to patients with classical POEMS syndrome published previously (Table 3) [15]. The median ages at diagnosis were both 47 for our cohort and POEMS prototype. The prevalence of peripheral neuropathy was more prevalent among our patients due to selection bias. As for organomegaly, hepatomegaly, splenomegaly, and lymphadenopathy were documented in 46%, 77% and 62% POEMS variants, respectively, which showed no significant difference in comparison with POEMS prototypes. Edema,

Table 2 Clinical and VEGF response of enrolled patients

No.	Tx	Clinical response	ONLS at diagnosis	ONLS 3 months after treatment/ transplant	ONLS 6 months after treatment/ transplant	ONLS at last visit	Organo-megaly	Extra-vascular overload	VEGF at diagnosis	VEGF lowest	M-relapse	C-relapse	VEGF-relapse
1	ASCT	Ic	7	7	4	4	R	R	6617	350	\	\	Y
2	ASCT	Ic	4	5	4	2	R	R	3467	1140	\	\	Y
3	Novel agent	Ic	5	NA	4	3	R	R	2581	NA	\	\	\
4	ASCT	Ic	4	3	NA	3	R	R	5375	40	Y	\	\
5	ASCT	Ic	5	5	2	2	R	R	6331	705	\	\	\
6	Melphelan	Ic	5	1	1	1	NS	NS	5525	701	\	Y	
7	ASCT	Ic	4	4	NA	4	R	R	6050	207	\	\	\
8	Radio-therapy	Ic	9	4	4	4	R	R	2155	1387	\	\	\
9	Novel agent	NA	2	NA	NA	NA	NA	NA	3478	NA	Y	\	\
10	None	NIc	9	NA	NA	9	NR	NR	3725	NA	\	\	\
11	Novel agent	Ic	1	1	1	1	R	NR	11,029	7927	\	\	\
12	ASCT	Ic	10	1	0	0	R	R	3217	622	\	\	\
13	Novel Agent	Ic	1	0	0	0	R	R	4998	1590	\	Y	Y

Abbreviations: *NA* not available, *NS* no such symptom, *Tx* treatment, *R* resolved, *NR* not resolved, *ASCT* autologous stem-cell transplant, *Novel agent* lenalidomide or thalidomide, *Ic* clinically improved, *NIc* clinically not improved, *VEGF* vascular epithelial growth factor, *M-relapse* emerging of M protein by serum protein electrophoresis, serum immunofixation electrophoresis or serum immunoglobulin free light chains assay during follow-up, *C-relapse* persistence, exacerbation, or newly onset of symptoms attribute to POEMS syndrome, *VEGF-relapse* increased VEGF level by 50% of in comparison with the latest VEGF level

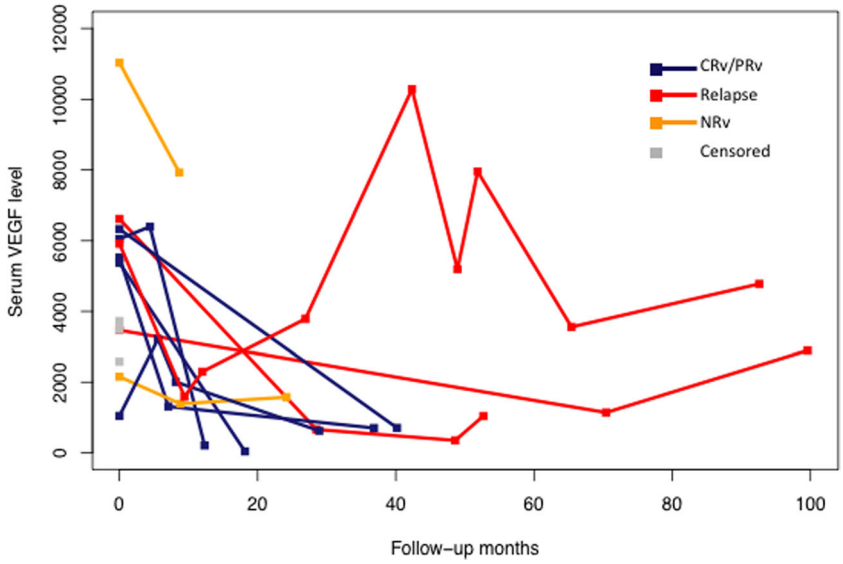

Fig. 1 Baseline and follow-up measurements of VEGF level showing changes with treatment

ascites, and pleural effusion were present in 77%, 46% and 58% of recruited patients, and 15% and 68% of previously reported POEMS patients. Other common clinical manifestations, such as, endocrinopathy, osteosclerosis, pulmonary hypertension, papilledema, thrombocytosis, and polycythemia affected a similar percentage of patients between our patients and reported typical cases. The median level of serum VEGF in the POEMS variants recruited was 4998 pg/ml (range 2155–11,029), similar to that of prototypes, which was 4040 pg/ml (range 111–23,782).

Discussion

We reported a series of 13 patients with clinical patterns highly resembled POEMS syndrome, with the exception that no demonstrable monoclonal gammopathy detected by conventional techniques. We summarized patients' symptoms and serum VEGF changes pre- and post-treatment. Considering such clinical characteristics and responsiveness to therapies targeting plasma cells, we suggested a novel variant of POEMS syndrome with undetectable M protein.

Hypotheses have been raised to explain the absence of monoclonal gammopathy of the variant POEMS syndrome. Limitation of measurements may fail to identify trace amount of M protein. The detection limit of sPEP for M protein is 0.3–0.7 g/dL, and that of sIFE is about 0.1 g/dL [16]. sFLC was introduced with significantly increased sensitivity [17, 18]. The combination of sIFE and sFLC increased the detection rate up to 99–100% for multiple myeloma, Waldenström macroglobulinemia, smoldering multiple myeloma, and immunoglobulin light chain (AL) amyloidosis [18, 19]; however, the ratio of FLCR is normal in all but 13–18% POEMS patients, making sFLC ineffective in identifying POEMS patients [14]. As there were two main assay kits used routinely for FLC testing, which are based on monoclonal (N latex FLC, Siemens, Marburg, Germany) and polyclonal (Freelite, The Binding Site, Birmingham, UK) antibodies with nephelometry or turbidimetry technologies, respectively, further applying both FLC test system may help in identifying FLC and thus the presence of a monoclonal paraprotein.

Thus, the presence of secretory plasma cells, which were too small to be tested, causes symptoms due to overproduction of cytokines such as VEGF, or other underlying pathogenesis. Surveillance for M protein for enrolled patients found two patients with emerging monoclonal gammopathy, indicating such a variant of POEMS has the potential to progress into the prototype.

Our series of POEMS cases with undetectable monoclonal plasma cells suggested that negative results in bone marrow biopsy were not enough to reject the diagnosis of POEMS [7, 8]. For example, Liang et al. reported a case of a 58-year-old male with polyneuropathy, organomegaly, pleural effusion, and hypothyroidism, and diagnosis was made based on bone lesion biopsy confirming the light-chain restriction [9]. Additional bone scans using CT, magnetic resonance imaging (MRI), and F-FDG PET/CT scan may prove to be contributive in identifying affected bone lesions feasible for guided biopsy or even surgical procedures, and therefore the confirmation of diagnosis [20]. We suggested a diagnosis of POEMS variant could be made with caution for patients with typical clinical manifestation, markedly elevated serum VEGF levels, and difficulties/contraindications to do bone lesion biopsy, who had rule out of other possible diagnoses carefully as well.

POEMS syndrome was considered as a model of a spectrum of diseases: from osteosclerotic myeloma to POEMS syndrome and to Castleman disease (CD) [21]. Here, we described a series of patients with multisystem involvement resemble the manifestation of POEMS with or without a confirmation of CD by

Table 3 Comparison between prototype of POEMS syndrome and no-M variant by clinical manifestations

	POEMS variants $N = 13$	Prototype of POEMS (Wang et al.[15]) $N = 362$	P value*
Age at symptom presenting	Median, 44 (25–57)	NA	NA
Age at diagnosis	Median, 47 (26–58)	Median, 47 (21–74)	NA
Male sex	6 (46%)	224 (62%)	0.2618
Polyneuropathy	13 (100%)	114 (31%)	< 0.001
Motor	13 (100%)	NA	NA
Sensor	13 (100%)	NA	NA
Total	Mean, 5.1 (1–10)	NA	NA
Organomegaly	13 (100%)	NA	NA
Hepatomegaly	6 (46%)	171 (47%)	1
Splenomegaly	10 (77%)	243 (67%)	0.5596
Lymphadenopathy	11 (85%)	235 (65%)	0.2333
Castleman disease confirmed by biopsy	3 (75%)	53 (64%)	1
Endocrinopathy	12 (92%)	NA	NA
Diabetes mellitus	4 (31%)	54 (15%)	0.125
Hypothyroidism	8 (62%)	246 (68%)	0.7635
Skin changes	12 (92%)	NA	NA
Hyperpigmentation	12 (92%)	322 (89%)	1
Glomeruloid hemangioma	7 (54%)	188 (52%)	1
Extravascular fluid overload	13 (100%)	NA	NA
Edema	10 (77%)	310 (86%)	0.4168
Ascites	6 (46%)	181 (50%)	1
Pleural effusion	7 (58%)	144 (40%)	0.3905
Serum VEGF level at diagnosis (pg/ml)	Median, 4998 (2155-11,029)	Median, 4040 (111–23,782)	NA
Bone lesion	9(69%)	NA	NA
Osteosclerotic	6 (46%)	199 (55%)	0.5798
Osteolytic	2(15%)	NA	NA
Mixed	1(8%)	NA	NA
β-CTX at diagnosis (ng/ml)	Mean, 1.35 (0.707–3.4)	NA	NA
Pulmonary hypertension	2 (22%)	68 (20%)	0.5862
Papilledema	8 (62%)	192 (53%)	0.5857
Thrombocytosis	5 (38%)	184 (51%)	0.4125
Polycythemia	3 (23%)	54 (15%)	0.4276
Anemia	1 (8%)	NA	NA
eGFR, < 60 ml/min	1 (8%)	21 (6%)	0.5503
Plasma cells in BM %	(0–3.5%)**	Median, 2% (0–16%)	NA

Abbreviation: *NA* not available, *ACTH* adrenocorticotropic hormone, *VEGF* vascular epithelial growth factor, *eGFR* estimated glomerular filtration rate, *BM* bone marrow, *IVIG* intravenous immunoglobulin

*Fisher exact test or Chi-square tests were applied

**Detailed information on bone marrow smear can be found in Table 1

lymph node biopsy, which may raise debates over the classification between POEMS variants with undetectable M-protein versus multicentric Castleman disease (MCD) variants with peripheral neuropathy and elevated VEGF. An overlap between two identities may be because the diagnosis of MCD relies on the pathological confirmation, while the diagnosis of POEMS variants relies mainly on symptoms and laboratory findings. Several published cases of Castleman disease with "interesting features" are actually likely cases of POEMS syndromes, which made the nomination more obscured [22–24]. Further studies on the pathogenesis of MCD or POEMS may help in subdivision differentiation. No matter either way, regimens targeting plasma cells are proved to be effective in both MCD variants and POEMS variants.

Since recognition of the variant of POEMS syndrome further challenges current diagnosing criteria, the value of elevated VEGF levels in the diagnosing of POEMS should be reconsidered. Watanabe et al. proposed that VEGF might increase the permeability of blood-neural barrier, resulting in elevated endoneural pressure and increased neurotoxic components, which finally lead to neural damage [25, 26]. In addition, due to the angiogenesis role of VEGF, the spleen, liver, and lymph nodes enlarged with marked vascular proliferation [25]. Angiogenesis of skin vessels may explain the finding of hemangiomata in POEMS patients. [27] To date, the significance of increased VEGF remains unclear, but may provide better understanding of the pathogenesis of POEMS syndrome, and may be of a higher value in diagnosing and monitoring.

Although we made a rather comprehensive description of the no-M POEMS variants, there still were several limitations. First, POEMS syndrome is a rare plasma cell disorder, and we were only able to recruit 13 variants for analysis. A larger sample size and a longer follow-up time may provide more convincing information on baseline characteristics, response to treatment, and make subtype analysis and multivariable analysis possible. Second, system involvement and baseline evaluation was incomplete for some enrolled patients. For example, β-CTX was missing for one patient at baseline, and three patients did not receive echocardiography. As POEMS syndrome is a multi-system disorder, a structured, validated, and efficient measurement recommendation checklist is desired for better description and evaluation in the future.

In conclusion, we described a group of patients with clinical manifestations highly resembling POEMS syndrome except for no evidence of monoclonal gammopathy. A variant form of POEMS syndrome was suggested according to characteristic constellations, elevated VEGF levels, and responsiveness to therapies directly targeting plasma cells. Elevated VEGF levels may help in teasing out such variants of POEMS syndrome.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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