Clinical spectrum of Castleman disease—associated neuropathy

Elie Naddaf, MD
Angela Dispenzieri, MD
Jay Mandrekar, PhD
Michelle L. Mauermann,
MD

Correspondence to
Dr. Mauermann:
mauermann.michelle@mayo.edu

ABSTRACT

Objective: To define the peripheral neuropathy phenotypes associated with Castleman disease.

Methods: We conducted a retrospective chart review for patients with biopsy-proven Castleman disease evaluated between January 2003 and December 2014. Patients with associated peripheral neuropathy were identified and divided into 2 groups: those with Castleman disease without POEMS syndrome (CD-PN) and those with Castleman disease with POEMS syndrome (CD-POEMS). We used a cohort of patients with POEMS as controls. Clinical, electrodiagnostic, and laboratory characteristics were collected and compared among patient subgroups.

Results: There were 7 patients with CD-PN, 20 with CD-POEMS, and 122 with POEMS. Patients with CD-PN had the mildest neuropathy characterized by predominant sensory symptoms with no pain and mild distal sensory deficits (median Neuropathy Impairment Score of 7 points). Although both patients with CD-POEMS and patients with POEMS had a severe sensory and motor neuropathy, patients with CD-POEMS were less affected (median Neuropathy Impairment Score of 33 and 66 points, respectively). The degree of severity was also reflected on electrodiagnostic testing in which patients with CD-PN demonstrated a mild degree of axonal loss, followed by patients with CD-POEMS and then those with POEMS. Demyelinating features, defined by European Federation of Neurologic Societies/Peripheral Nerve Society criteria, were present in 43% of the CD-PN, 78% of the CD-POEMS, and 86% of the POEMS group.

Conclusion: There is a spectrum of demyelinating peripheral neuropathies associated with Castleman disease. CD-PN is sensory predominant and is the mildest phenotype, whereas CD-POEMS is a more severe sensory and motor neuropathy. Compared to the POEMS cohort, those with CD-POEMS neuropathy have a similar but less severe phenotype. Whether these patients respond differently to treatment deserves further study. *Neurology*® 2016;87:2457-2462

GLOSSARY

CD-PN = Castleman disease with peripheral neuropathy only; **CD-POEMS** = Castleman disease with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; **IL-6** = interleukin-6; **NIS** = Neuropathy Impairment Score; **POEMS** = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; **PMTA** = peroneal motor amplitude recording from the tibialis anterior muscle; **TANES** = tibialis anterior needle examination score; **VEGF** = vascular endothelial growth factor.

Castleman disease is a rare lymphoproliferative disorder characterized by enlarged lymph nodes and a broad spectrum of clinical manifestations. Although Castleman disease is divided in 3 pathologic types (hyaline vascular, plasma cell, and mixed),¹ the clinical phenotype is driven more by whether the lymphadenopathy is unicentric (confined to one region) or multicentric. Patients with multicentric disease will most often present with constitutional symptoms,²⁻⁴ reflecting the excessive proinflammatory cytokinemia.⁵ Furthermore, interleukin-6 (IL-6) is thought to play a major role in the pathogenesis of Castleman disease.⁶⁻⁸

Castleman disease can be associated with peripheral neuropathy,^{9,10} more commonly in multicentric Castleman disease.¹¹ The presence or absence of peripheral neuropathy is thought to be important in the classification of the disease because patients with peripheral neuropathy tend to have relatively different characteristics and might require a different therapeutic

Supplemental data
at Neurology.org

From the Departments of Neurology (E.N., M.L.M.), Internal Medicine (A.D.), and Medicine (J.M.), Mayo Clinic, Rochester, MN.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

approach.^{11–13} Castleman disease can also have coexisting polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome.^{14,15} However, little is known about the specific clinical and electrodiagnostic characteristics of the peripheral neuropathy phenotypes associated with Castleman disease with or without POEMS syndrome. Furthermore, there is no comparison of the peripheral neuropathy in POEMS syndrome with and without Castleman disease. Therefore, we sought to better define the clinical, laboratory, and electrodiagnostic characteristics of the peripheral neuropathy in these 3 conditions by retrospective chart review.

METHODS Patient selection. We searched the Mayo Clinic computerized database for patients seen between January 2003 and December 2014 who had the diagnosis of biopsy-proven Castleman disease.¹⁵ We included patients who had tissue specimens reviewed by the Mayo Clinic Department of Pathology. Patients were also required to have a diagnosis of peripheral neuropathy. We excluded patients with an alternative cause of peripheral neuropathy such as diabetes mellitus, advanced kidney disease, excessive alcohol intake, or vitamin B₁₂ deficiency. Patients were then divided into 2 groups, depending on the association with POEMS syndrome. POEMS syndrome diagnosis was based on the diagnostic criteria published in 2003.¹⁶ We identified POEMS controls without Castleman disease from our prior study.¹⁷ Therefore, 3 groups of patients were compared: those with Castleman disease with peripheral neuropathy and without POEMS (CD-PN), those with Castleman disease with POEMS (CD-POEMS), and patients with POEMS syndrome (POEMS). Clinical, laboratory, and electrodiagnostic information was extracted by retrospective chart review. We included only vascular endothelial growth factor (VEGF) levels, IL-6 levels, and platelet counts obtained before treatment in the analysis. Thrombocytosis was defined as a platelet count >450,000/ μ L.

Scoring of neuropathy severity. The Neuropathy Impairment Score (NIS) was used to score the severity of the peripheral neuropathic deficits.¹⁸ In brief, the NIS is a summed score of a standard and representative list of motor, sensory, and muscle stretch reflex impairments. Scores range from 0 (normal) to 4 (paralyzed) points for motor and 0 to 2 (absent) points for sensation and reflexes for individual attributes. For patients 50 to 69 years old, ankle reflexes are graded 0 points when decreased (considered normal) and 1 point when absent. For patients $\geq$ 70 years old, absent or decreased ankle reflexes are graded 0 points. Total NIS ranges from 0 to 244 points, NIS-weakness from 0 to 192 points, NIS-sensory from 0 to 32 points, and NIS-reflexes from 0 to 20 points. The NIS was calculated from the abstraction of findings from the neurologic examination form at Mayo Clinic visits.

Electrodiagnostic testing. The assessment of nerve conduction studies and EMG used methods standard for the EMG laboratory at Mayo Clinic. We used the European Federation of Neurologic Societies/Peripheral Nerve Society electrodiagnostic criteria to

determine whether the peripheral neuropathy was demyelinating.¹⁹ The severity of the neuropathy from an electrodiagnostic standpoint was estimated by the degree of axonal loss. We used percentiles and calculated a composite amplitude score of the sural sensory, tibial motor (recording from the abductor hallucis muscle), and peroneal motor (recording from the extensor digitorum brevis muscle) responses. Percentiles were calculated from the Rochester Diabetic Study healthy cohort and corrected for anthropometric characteristics.^{20,21} In the lower limb, nerve conduction studies are usually performed by recording from the foot. In severe cases, the responses are commonly absent, limiting further analysis. Hence, we used the peroneal motor amplitude recording from the tibialis anterior muscle (PMTA), along with electromyographic findings from this muscle, to compare the CD-POEMS and POEMS groups. Given the unavailability of detailed normative data for proximal nerve conduction studies, we used PMTA values rather than percentiles. We also calculated a tibialis anterior needle examination score (TANES) by summing abnormalities of fibrillation potentials, long-duration motor unit potentials, and reduced recruitment using standard grading. For further validation, we analyzed the correlation between the PMTA and TANES.

Statistical analysis. Descriptive summaries are presented as frequencies and percentages for categorical variables and median and ranges for continuous variables. Comparisons among the 3 groups were performed with the Kruskal-Wallis, χ^2 , or Fisher exact test as appropriate. All of the tests were 2 sided. When the *p* value comparing the 3 groups reached statistical significance (<0.05), groups were then compared by pairs with the Wilcoxon rank sum, χ^2 , or Fisher exact test as appropriate.

Standard protocol approvals, registrations, and patient consents. Mayo Clinic Investigational Review Board approved the study. We included patients who had given consent allowing their medical records to be used for research purposes.

RESULTS Patient characteristics. One hundred five patients with biopsy-proven Castleman disease were identified (figure e-1 at [Neurology.org](#)). Twenty-seven patients had an associated peripheral neuropathy: 7 with CD-PN and 20 with CD-POEMS. One hundred twenty-two patients with POEMS (without Castleman disease) served as controls. Patients in all 3 groups were more commonly men; however, there was no difference in age, sex, height, and weight among the 3 groups (table 1). Among patients with Castleman disease, 19 patients had the histopathologic type reported, with plasma cell type being the most common (42%), followed by hyaline vascular (37%) and mixed (21%; table 1).

Clinical presentation. Patients presented on average in their sixth decade. Patients with CD-POEMS had a longer duration of neuropathic symptoms before evaluation (table 2). At presentation to our institution, patients with CD-PN reported mainly distal lower limb numbness with no pain. Approximately half of the patients reported paresthesias and weakness. In contrast, most patients with CD-POEMS and patients with POEMS presented with numbness, paresthesias,

Table 1 Patient demographics and disease characteristics

Parameter	CD-PN (n = 7)	CD-POEMS (n = 20)	POEMS (n = 122)	p Values
Age, y	56 (40-66)	53 (33-72)	53 (20-83)	NS
Female, %	43	35	40	NS
Multicentric/unicentric, n	6/1	19/1	—	NS
Pathology type: HV/PC/mixed, n	2/1/2 (n = 5)	5/7/2 (n = 14)	—	NS
Serum heavy chain: IgG or IgA/IgM, n	—	16/0	111/2	NS
Light chain: κ/λ , n	—	1/18	2/119	NS
Quantifiable M-spike, n	—	6	83	0.0021
M-spike, g/dL	—	0.7 (0.001-1.4)	0.7 (0.001-2.4)	NS

Abbreviations: CD = Castleman disease; HV = hyaline vascular; NS = not significant; PC = plasma cell; PN = peripheral neuropathy.

Values are displayed as median and ranges for continuous variables and percentages for categorical variables. NS = > 0.05

and weakness, and more than half of the patients reported pain, often necessitating neuropathic pain medications and sometimes opioids. The pain was described as burning, shooting, or stabbing pain.

Neurologic examination. Patients with CD-PN had mild, predominantly sensory deficits in a length-dependent pattern, involving mainly the distal lower limbs. Only one patient with CD-PN had associated distal weakness. Conversely, patients with CD-POEMS and POEMS had more severe motor and sensory deficits in either a length-dependent pattern or a polyradiculoneuropathy. Among the 3 groups, the CD-PN group had the mildest neuropathy. The CD-POEMS group had a less severe neuropathy than the POEMS group (figure 1).

Electrodiagnostic testing. On nerve conduction studies, respective rates of definite and possible demyelination were as follows: CD-PN, 43% and 0%; CD-POEMS, 56% and 22%; and POEMS control, 51% and 35% (figure 2A). Regarding

the severity of the neuropathy estimated by the amount of axonal loss, the composite amplitude score was greatest in CD-PN, followed by CD-POEMS and POEMS (figure 2B). The CD-POEMS group had a greater PMTA (figure 2C) and a lower TANES (figure 2D). The PMTA correlated with the TANES (correlation coefficient -0.6638 , $p < 0.0001$).

Laboratory findings. In both the CD-POEMS and POEMS groups, the plasma cell disorder was almost always lambda-restricted and of non-IgM isotype (table 1). VEGF levels were elevated in 3 of 4 patients with CD-PN, 13 of 14 patients with CD-POEMS, and 18 of 23 patients with POEMS ($p > 0.05$). IL-6 levels were elevated in 2 of 3 patients with CD-PN, 5 of 10 patients with CD-POEMS, and 10 of 16 patients with POEMS ($p > 0.05$). Two of 6 patients with CD-PN, 7 of 17 patients with CD-POEMS, and 59 of 119 patients with POEMS had thrombocytosis ($p > 0.05$). The median VEGF levels, IL-6 levels, and platelet count did not differ among the 3 groups (table 3). There were no HIV- or human herpesvirus-8–positive patients in this cohort.

Table 2 Neuropathy symptoms at presentation

Parameter	CD-PN (n = 7)	CD-POEMS (n = 20)	POEMS (n = 122)	p Values
Duration of neuropathic symptoms, mo	15 (12-72)	48 (5-132)	15 (1-120)	0.0058
Weakness, n (%)	3 (43)	14 (70)	113 (93)	0.0004
Numbness, n (%)	6 (86)	19 (95)	97 (80)	NS
Paresthesias, n (%)	4 (57)	17 (85)	89 (73)	NS
Neuropathic pain, n (%)	0 (0)	11 (55)	67 (55)	0.0327
Neuropathic pain medication, n (%)	1 (14.3)	10 (50)	55 (45)	NS
Opioid use, n (%)	0 (0)	3 (15)	30 (25)	NS

Abbreviations: CD = Castleman disease; PN = peripheral neuropathy.

NS = >0.05.

DISCUSSION In our cohort, 27.5% of patients with Castleman disease had an associated peripheral neuropathy with or without POEMS syndrome. This percentage is nearly identical to that reported in a previous cohort of patients seen between 1948 and 2002: 9% with CD-PN and 18% with CD-POEMS.¹¹ The peripheral neuropathies of Castleman disease and POEMS represent a spectrum in which CD-PN is the mildest, often purely sensory, and without pain. Although CD-POEMS and POEMS share a severe, commonly painful, sensory and motor peripheral neuropathy or polyradiculoneuropathy, POEMS is more severe clinically and electrophysiologically. This difference is not accounted for by lead time bias. It should be noted that in patients with

Figure 1 Neuropathy Impairment Score (NIS) score box plots

(A) Total NIS score. Castleman disease with peripheral neuropathy (CD-PN) without POEMS, median 7 (range 0-69); Castleman disease with POEMS (CD-POEMS), 33 (6-115.5); POEMS, 66 (4-168) ($p < 0.0001$; $p_1 = 0.0078$; $p_2 = 0.0002$; $p_3 = 0.0008$). (B) NIS-weakness (NIS-W): CD-PN, 0 (0-45); CD-POEMS, 14 (0-79.5); POEMS, 40 (0-136) ($p < 0.0001$; $p_1 = 0.022$; $p_2 = 0.0004$; $p_3 = 0.0015$). (C) NIS-reflexes (NIS-R): CD-PN, 2 (0-20); CD-POEMS, 12 (0-20); POEMS, 20 (0-20) ($p < 0.0001$; $p_1 = 0.0251$; $p_2 = 0.0004$; $p_3 = 0.0029$). (D) NIS-sensory (NIS-S): CD-PN, 4 (0-10); CD-POEMS, 10 (1-18); POEMS, 10 (2-30) ($p = 0.0198$; $p_1 = 0.0340$; $p_2 = 0.0051$; $p_3 > 0.05$). Dark horizontal lines show the median; black diamonds, mean. p Values: p , 3-group comparison; p_1 , CD-PN vs CD-POEMS; p_2 , CD-PN vs POEMS; and p_3 , CD-POEMS vs POEMS.

POEMS syndrome, including CD-POEMS, the peripheral neuropathy is usually the predominant feature of the illness. However, in patients with CD-PN, the peripheral neuropathy might be overlooked given the mild nature of the symptoms and signs. In this cohort, the number of patients with CD-PN may be underestimated because patients with subjective sensory symptoms without further evaluation were not included.

Several hematologic disorders such as monoclonal gammopathy of undetermined significance, POEMS syndrome, and Waldenström macroglobulinemia can be associated with a peripheral neuropathy with demyelinating features.^{17,22,23} An interesting finding in this study is that Castleman disease without POEMS is an additional cause of a demyelinating neuropathy. This may be an important clue to diagnosis and adds to the utility of performing electrodiagnostic studies in chronic sensory neuropathies. In our cohort, the percentage of patients with demyelination may even be underestimated because it is common to have absent responses in the lower limbs, which hinders further characterization. In addition, according to the European Federation of Neurologic Societies/

Peripheral Nerve Society joint task force,¹⁹ if the demyelination criteria were not fulfilled by testing one side, testing the other side is then recommended, which is not always done in clinical practice.

The elevation of VEGF and IL-6 levels serves as an important clue to these disorders; therefore, VEGF and IL-6 levels should be tested. However, the degree of abnormality does not correlate with a specific condition. This finding is not unexpected because our prior studies have not shown VEGF to correlate with disease severity.²⁴ Nonetheless, as we and others have previously demonstrated, elevations in these cytokines, VEGF in particular, can help differentiate POEMS, and now CD-PN, from other causes of demyelinating peripheral neuropathy.^{25,26}

We have demonstrated that these disorders represent a spectrum, with CD-PN having a mild distal sensory predominant neuropathy that differs from the severe sensory and motor peripheral neuropathy or polyradiculoneuropathy associated with coexisting POEMS syndrome. Both of these neuropathies often have demyelinating characteristics on electrodiagnostic testing that can serve as a clue to the diagnosis. Testing for VEGF and IL-6 may

Figure 2 Electrodiagnostic testing

allow earlier recognition of these disorders. In addition, patients with CD-POEMS have a relatively milder peripheral neuropathy compared to patients with POEMS without Castleman disease, both

clinically and on electrodiagnostic testing. This is a novel discovery that deserves further study to evaluate whether the prognosis or treatment response in CD-POEMS and POEMS differs.

Table 3 Laboratory findings

Laboratory test	CD-PN		CD-POEMS		POEMS		p Value
	Median	Range	Median	Range	Median	Range	
VEGF, pg/mL	367.5 (n = 4)	49–2030	389 (n = 14)	61–2033	303 (n = 23)	31–1987	NS
IL-6, pg/mL	11.6 (n = 3)	4.03–13.24	5.5 (n = 10)	2.05–28.28	6.6 (n = 11.6)	2.4–40.6	NS
Platelet count, $\times 10^6/L$	342,000 (n = 6)	164,000–804,000	434,000 (n = 17)	165,000–730,000	443,000 (n = 119)	14,000–1,163,000	NS

Abbreviations: CD = Castleman disease; IL-6 = interleukin-6; PN = peripheral neuropathy; VEGF = vascular endothelial growth factor. NS = >0.05 .

Normal values: VEGF, 31 to 86 pg/mL; IL-6, 0.31 to 5 pg/mL; and platelet count, 150 to $450 \times 10^6/L$.

AUTHOR CONTRIBUTIONS

Study concept and design: Dr. Naddaf, Dr. Dispenzieri, and Dr. Mauermann. Acquisition of data: Dr. Naddaf. Data analysis and interpretation: all authors. Statistical plan and analysis: Dr. Naddaf and Dr. Mandrekar. Drafting the manuscript: Dr. Naddaf. Critical revision of the manuscript for important intellectual content: all authors. Study supervision: Dr. Mauermann.

ACKNOWLEDGMENT

The authors thank Dr. William Litchy for his thoughtful review of the manuscript and Jenny Davies for her assistance in calculating nerve conduction percentile values.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received April 28, 2016. Accepted in final form September 8, 2016.

REFERENCES

1. Keller AR, Hochholzer L, Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. *Cancer* 1972;29:670–683.
2. Frizzera G, Banks PM, Massarelli G, Rosai J. A systemic lymphoproliferative disorder with morphologic features of Castleman's disease: pathological findings in 15 patients. *Am J Surg Pathol* 1983;7:211–231.
3. Weisenburger DD, Nathwani BN, Winberg CD, Rappaport H. Multicentric angiofollicular lymph node hyperplasia: a clinicopathologic study of 16 cases. *Hum Pathol* 1985;16:162–172.
4. Dispenzieri A, Armitage JO, Loe MJ, et al. The clinical spectrum of Castleman's disease. *Am J Hematol* 2012;87:997–1002.
5. Fajgenbaum DC, van Rhee F, Nabel CS. HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy. *Blood* 2014;123:2924–2933.
6. Yoshizaki K, Matsuda T, Nishimoto N, et al. Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. *Blood* 1989;74:1360–1367.
7. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood* 2005;106:2627–2632.
8. Brandt SJ, Bodine DM, Dunbar CE, Nienhuis AW. Retroviral-mediated transfer of interleukin-6 into hematopoietic cells of mice results in a syndrome resembling Castleman's disease. *Curr Top Microbiol Immunol* 1990;166:37–41.
9. Yu GS, Carson JW. Giant lymph-node hyperplasia, plasma-cell type, of the mediastinum, with peripheral neuropathy. *Am J Clin Pathol* 1976;66:46–53.
10. Mallory A, Spink WW. Angiomatous lymphoid hamartoma in the retroperitoneum presenting with neurologic signs in the legs. *Ann Intern Med* 1968;69:305–308.
11. Nakanishi T, Sobue I, Toyokura Y, et al. The Crow-Fukase syndrome: a study of 102 cases in Japan. *Neurology* 1984;34:712–720.
12. Hineman VL, Philyly RL, Banks PM. Angiofollicular lymph node hyperplasia and peripheral neuropathy: association with monoclonal gammopathy. *Mayo Clin Proc* 1982;57:379–382.
13. Menke DM, Camoriano JK, Banks PM. Angiofollicular lymph node hyperplasia: a comparison of unicentric, multicentric, hyaline vascular, and plasma cell types of disease by morphometric and clinical analysis. *Mod Pathol* 1992;5:525–530.
14. Bardwick PA, Zvaifler NJ, Gill GN, Newman D, Greenway GD, Resnick DL. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS syndrome: report on two cases and a review of the literature. *Medicine* 1980;59:311–322.
15. Cronin DMP, Warnke RA. Castleman disease: an update on classification and the spectrum of associated lesions. *Adv Anat Pathol* 2009;16:236–246.
16. Dispenzieri A, Kyle RA, Lacy MQ, et al. POEMS syndrome: definitions and long-term outcome. *Blood* 2003;101:2496–2506.
17. Mauermann ML, Sorenson EJ, Dispenzieri A, et al. Uniform demyelination and more severe axonal loss distinguish POEMS syndrome from CIDP. *J Neurol Neurosurg Psychiatry* 2012;83:480–486.
18. Dyck PJ, Sherman WR, Hallcher LM, et al. Human diabetic endoneurial sorbitol, fructose, and myo-inositol related to sural nerve morphometry. *Ann Neurol* 1980;8:590–596.
19. Van den Bergh PY, Hadden RD, Bouche P, et al. EFNS/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society—first revision. *J Peripher Nerv Syst* 2010;15:1–9.
20. Dyck PJ, Davies JL, Wilson DM, Service FJ, Melton LJ, O'Brien PC. Risk factors for severity of diabetic polyneuropathy: intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study cohort. *Diabetes Care* 1999;22:1479–1486.
21. Dyck PJ, O'Brien PC, Litchy WJ, Harper CM, Daube JR. Use of percentiles and normal deviates to express nerve conduction and other test abnormalities. *Muscle Nerve* 2001;24:307–310.
22. Mauermann ML. Paraproteinemic neuropathies. *Continuum* 2014;20:1307–1322.
23. Klein CJ, Moon J-S, Mauermann ML, et al. The neuropathies of Waldenström's macroglobulinemia (WM) and IgM-MGUS. *Can J Neurol Sci* 2011;38:289–295.
24. Karam C, Klein CJ, Dispenzieri A, et al. Polyneuropathy improvement following autologous stem cell transplantation for POEMS syndrome. *Neurology* 2015;84:1981–1987.
25. Watanabe O, Arimura K, Kitajima I, Osame M, Maruyama I. Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome. *Lancet* 1996;347:702.
26. D'Souza A, Hayman SR, Buadi F, et al. The utility of plasma vascular endothelial growth factor levels in the diagnosis and follow-up of patients with POEMS syndrome. *Blood* 2011;118:4663–4665.