POEMS Syndrome: A Case Highlighting the Challenges in Diagnosis

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Abstract

POEMS syndrome is a multisystem disorder characterized by polyneuropathy, organomegaly, endocrinopathy, and skin changes in the context of a monoclonal plasma cell disorder. While these features may appear in the syndrome, they do not always occur simultaneously and can present with multiple other symptoms. A thorough laboratory and radiological workup is recommended to assess for multisystem involvement, and a bone marrow or skeletal lesion biopsy may be necessary to confirm an underlying plasma cell disorder. Given the wide range of possible presentations, diagnosing POEMS can be challenging and may be confused with CIDP or smoldering myeloma. However, maintaining a high clinical suspicion this syndrome, even when not all features are present, is crucial for a timely diagnosis and optimal treatment, particularly for neurological recovery. We present the case of a 57-year-old male with progressive sensorimotor weakness who was initially diagnosed with CIDP but ultimately found to have POEMS syndrome, based on elevated VEGF levels, IgG lambda monoclonal gammopathy, sclerotic bone lesions, skin changes, endocrinopathy, and a biopsy-proven plasmacytoma.

Introduction

POEMS syndrome is a paraneoplastic, multisystem disorder that occurs in the setting of an underlying plasma cell disorder.[1] Although the acronym implies the presence of polyneuropathy, organomegaly, endocrinopathy, a monoclonal plasma cell disorder, and skin changes, not all of the features may be present, nor are they required to make the diagnosis.[2] Other features, such as elevated vascular endothelial growth factor (VEGF) levels, sclerotic bone lesions, Castleman disease, extravascular volume overload, and papilledema, may accompany the polyneuropathy and underlying monoclonal disorder and help fulfill the major and minor criteria to make the diagnosis (Table 1).

A thorough evaluation, including skin inspection, laboratory workup and testing such as a skeletal survey and bone marrow biopsy, is crucial to differentiate the syndrome from chronic inflammatory demyelinating polyneuropathy (CIDP), isolated monoclonal gammopathy of uncertain significance (MGUS), or smoldering multiple myeloma. This is important to avoid unnecessary treatment-related adverse events and to prevent further progression due to undertreatment. In this report, we present the case of a 57-year-old male with rapidly progressive demyelinating polyneuropathy, who was eventually diagnosed with POEMS syndrome, highlighting the diagnostic challenges associated with this condition.

Table 1. Diagnosis criteria for POEMS syndrome

Mandatory Major Criteria	Polyneuropathy (typically demyelinating)
	Monoclonal plasma cell-proliferative disorder (almost always λ)
Other Major Criteria	Castleman disease
	Sclerotic bone lesions
	Vascular endothelial growth factor elevation
Minor Criteria	Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	Extravascular volume overload (edema, pleural effusion, or ascites)
	Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
	Papilledema
	Thrombocytosis/polycythemia
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B12 values

*Both mandatory major criteria, one other major criterion, and one minor criterion need to be present to confirm the diagnosis

Case

A 57-year-old male with a 20-year history of rheumatoid arthritis (RA) presented with rapidly progressive weakness and numbness. Initially, he reported intermittent paresthesias in his soles. Over the next 4 months, he experienced mild difficulties with thumb extension and ankle plantar flexion. He developed bilateral foot drop, which progressed rapidly to complete ankle and toe paralysis over 2 months. During this time, he also experienced finger extension weakness, difficulty standing from a seated position, intense paresthesias and numbness in his hands and feet, and increasing difficulty with ambulation, eventually requiring a walker. He denied ocular, bulbar, respiratory, or autonomic symptoms, as well as pain. He reported an unintentional 40-pound weight loss over 6 months but no fever or night sweats. His RA had been well-controlled for years without recent medication or flare-ups. He was diagnosed with diabetes (hemoglobin A1C 7.2%) a few weeks earlier, as part of a neuropathy work-up.

On examination, he had moderate weakness in proximal muscles (Medical Research Council [MRC] scale 3 to 4) and severe weakness in distal upper extremity (MRC scale 1 to 2) and lower extremity (MRC scale 0) muscles. Sensory examination revealed absent vibration and proprioception at the ankles, and absent proprioception at the metacarpophalangeal joint, with decreased vibration at the wrist. Pinprick sensation was normal, and he had diffuse areflexia. He was unable to maintain a standing position and required a walker to ambulate.

Electrodiagnostic testing revealed a primarily demyelinating sensorimotor polyradiculoneuropathy with secondary axonal loss. The nerve conduction studies (NCS) showed severe axonal loss in the lower extremities and moderate axonal loss with prolonged latency, slowed conduction velocity, conduction block of greater than 30% and temporal dispersion in the right median and ulnar motor nerves (Table 2). There was active denervation in the distal muscles tested (Table 3).

Findings met definite 2021 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) CIDP electrodiagnostic criteria. Based on clinical presentation and electrodiagnostic findings, he was diagnosed with severe CIDP and was admitted for plasma exchange (PLEX).

Initial laboratory testing revealed a hemoglobin A1C of 7.2%, and an IgG lambda monoclonal gammopathy of 0.44 g/dL. Kappa and lambda light chains, and the free light chain (FLC) ratio were normal. VEGF was elevated at 446 pg/mL (normal range: 9–86 pg/mL). Otherwise, the sedimentation rate, C-reactive protein (CRP), TSH, vitamin B1 and B12, copper levels, complete blood count, and comprehensive metabolic panel were normal. Based on the laboratory results and the presence of demyelinating polyneuropathy, there was concern for POEMS syndrome.

Skin inspection revealed glomeruloid hemangiomata on the abdomen and peripheral edema in the lower extremities. A computed tomography (CT) scan of the chest, abdomen, and pelvis, with and without contrast, showed mixed lytic and sclerotic osseous lesions in the S1 and S2 sacral segments (Figure 1), as well as multiple small pelvic lymph nodes (within normal size limits) and small soft tissue retroperitoneal nodules.

Table 2. Nerve conduction study

Motor Nerve Conductions							
Nerve/Site	**Latency (ms)**	**Amplitude (mV)**	**Duration (ms)**	**Segments**	**Distance (mm)**	**Latency difference (ms)**	**CV (m/s)**
R Median-ABP							
Wrist	5.6	1.9	8.2	Wrist-ABP	70	5.6	
Elbow	21.1	1.3	11.7	Elbow-Wrist	270	15.5	17
R Ulnar-ADM							
Wrist	5.2	3.0	8.5	Wrist-ADM	70	5.2	
B. Elbow	12.9	2.0	23.5	B. Elbow-Wrist	210	7.6	27
A. Elbow	16.3	1.5	22.4	A. Elbow-B. Elbow	100	3.4	30
R Peroneal- EDB							
Ankle	NR	NR	NR	Ankle-EDB	80	NR	
R Peroneal- TA							
B. Fibular Head	NR	NR	NR	B. Fibular head-TA		NR	
R. Tibial- AH							
Ankle	Ankle	NR	NR	Ankle-AH	80	NR	
F Waves							
Nerve	**M Latency (ms)**			**F latency (ms)**			
R Median- ABP	NR			NR			
R Ulnar- ADM	NR			NR			
Sensory Nerve Conductions							
Nerve/Site	**Onset Latency (ms)**	**Peak Latency (ms)**	**Amplitude (uV)**	**Segments**	**Latency difference (ms)**	**Distance (mm)**	**CV (m/s)**
R Median-antidromic							
Wrist	3.6	4.4	5.4	Wrist- Digit II	3.56	130	36.5
R Ulnar-Antidromic							
Wrist	NR	NR	NR	Wrist- Digit V	NR	110	NR
R Radial-Anatomic Snuffbox							
Forearm	2.6	3.4	8.7	Forearm-Snuffbox	2.56	100	39.0
R Sural-Calf							
Lower leg	NR	NR	NR	Lower leg-ankle	NR	140	NR

* The upper and lower extremity temperature for this study was 32 ^{0}C
Abbreviations: ms, millisecond; mV, millivolts; mm, millimeter; m/s, meters per second; ABP, abductor pollicis brevis; ADM, abductor digiti minimi; EDB, extensor digitorum brevis; TA, tibialis anterior; AH, abductor hallucis; R, right; A, above; B, below; NR, no response

Table 3. Electromyography study

EMG Summary Table									
	Insertional	Spontaneous Activity			Volitional MUAPs				
Muscle	**Activity**	**Fibs**	**PSW**	**Fasc**	**Poly**	**Amp**	**Duration**	**Recruitment**	**Other**
R Tibialis Anterior	++	3+	3+	None					No MUPs observed
R Gastrocnemius	++	3+	3+	None					No MUPs observed
R Vastus medialis	++	3+	3+	None	++	Normal	+	Moderately decreased	None
R First Dorsal Interosseous	++	3+	3+	None	None	Normal	Normal	Severely decreased	None
R Deltoid	Normal	None	None	None	None	Normal	Normal	Moderately decreased	None

* Abbreviations: R, right; MUAP, motor unit action potentials; MUPs, motor unit potentials; Fibs, fibrillation potentials; PSW, positive sharp waves; Fasc, fasciculations; Poly, polyphasic potentials; Amp, amplitude

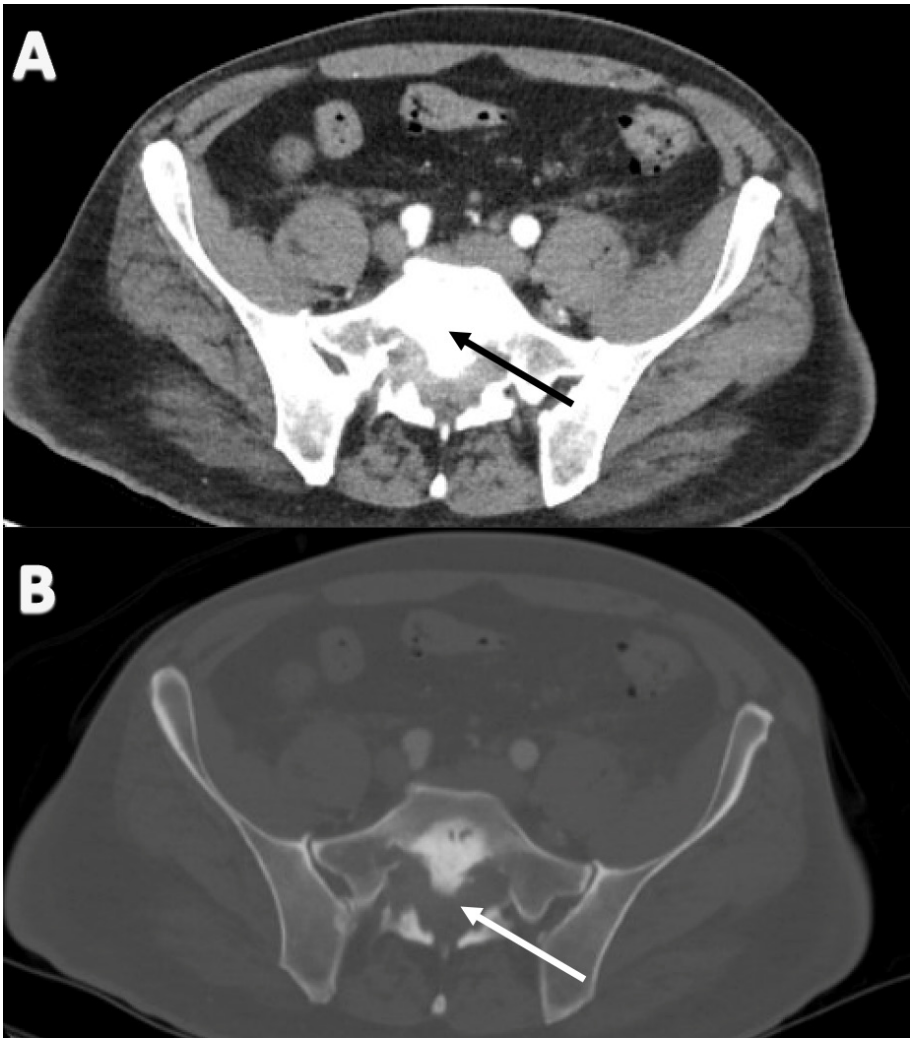

Figure 1: Computed tomography scan of the sacrum depicting mixed lytic and sclerotic lesions of the S1 and S2 sacral body. (A) Sclerotic component of the sacral body as noted by the hyperdense region (*black arrow*). (B) Lytic component of the sacral body as noted by the hypodense region (*white arrow*)

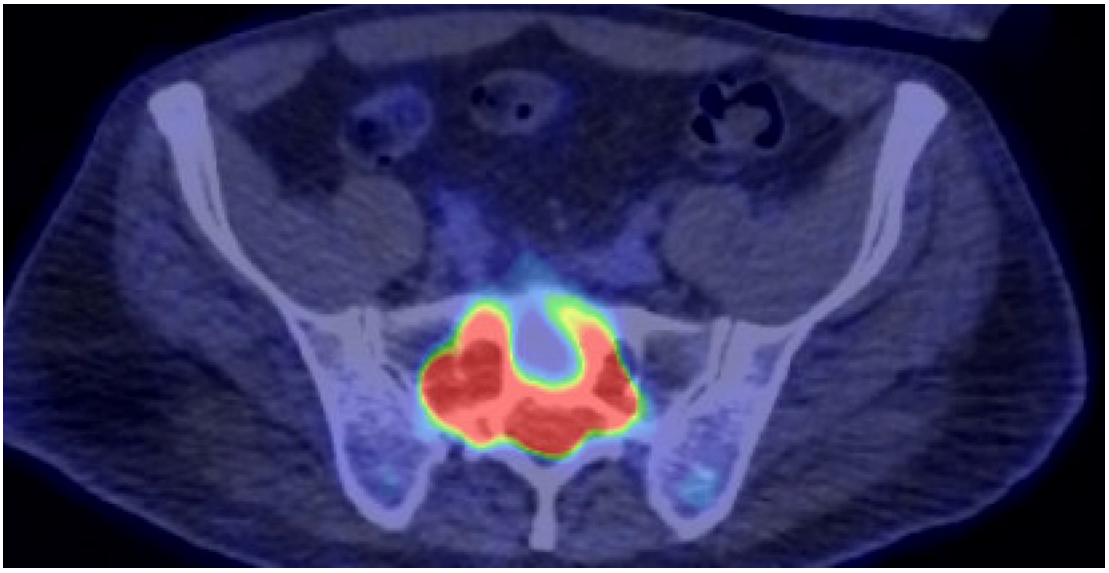

Figure 2: Nuclear medicine position emission tomography scan depicting increased fluorodeoxyglucose uptake involving the sacral lytic lesion.

Endocrinology labs revealed mild prolactin elevation and low testosterone levels. However, given the absence of symptoms and in the context of an acute illness, the endocrinology team did not consider these laboratory abnormalities clinically relevant to support a diagnosis of POEMS syndrome. A bone marrow biopsy was normal, and because of this, along with the lack of organomegaly and small paraprotein level, the hematology team was hesitant to diagnose POEMS syndrome.

A PET scan showed increase FDG uptake involving the lytic lesion mentioned (Figure 2), but no other areas of concern. The patient completed 5 sessions of PLEX with mild proximal strength improvement but worsening of finger extension and abduction strength. A biopsy of the sacral lytic lesion eventually revealed monoclonal lambda plasma cells, after which it was decided to proceed with radiotherapy targeting the isolated lytic lesion.

Discussion

Diagnosing POEMS syndrome can be challenging, but maintaining a high suspicion in patients with progressive sensorimotor demyelinating polyneuropathy and paraproteinemia, especially if refractory to immunotherapy, is crucial for ensuring appropriate and prompt treatment. Our patient met mandatory criteria for diagnosis (polyneuropathy and a monoclonal plasma cell proliferative disorder) along with two major criteria (elevated VEGF levels and sclerotic bone lesions) and two minor criteria (skin changes and peripheral edema – diabetes is not sufficient to fulfill the endocrinopathy criteria), thus confirming the diagnosis.[2]

One challenge in diagnosing POEMS is the misconception that patients must present all components of the acronym. The only mandatory features are polyneuropathy and a monoclonal plasmaproliferative disorder. In most cases, the polyneuropathy is progressive, length-dependent, sensorimotor, and refractory to immunotherapy, with electrodiagnostic testing showing demyelination and secondary axonal loss.[1] Compared to CIDP, NCS in POEMS typically shows greater axonal loss, more pronounced slowing of motor and sensory conduction velocities, less frequent temporal dispersion and conduction block, and absence of sural sparing.[1,3] Interestingly, the NCS of our patient showed temporal dispersion and conduction block. Although these findings are unusual in POEMS, their presence should not deter consideration of this diagnosis.

The monoclonal (M)-protein is almost always IgA or IgG lambda. In about 78% of cases, FLC ratio is normal, and the M-spike is usually small.[1,2] In one case series, the median paraprotein level was 1.1 g/dL, with 93% of patients having an M-spike of 2 g/dL or less, as in our case.[4] This is significant because an IgG M-protein level below 1.5 g/dL with a normal FLC ratio is considered low-risk for multiple myeloma and may be overlooked.[5]

The other features of the POEMS acronym are non-mandatory. Organomegaly affects 45% to 85% of patients and, when present, is typically mild.[2] Hemangiomas or telangiectasia occur in 9% to 35% of patients, as in our case, while other skin manifestations, such as hyperpigmentation, plethora, acrocyanosis, and hypertrichosis, are seen in 68% to 93% of cases.[2] Endocrinopathies are present in 66-96% of cases, with hypogonadism being the most common.[6] While diabetes is not considered part of the criteria due to its high prevalence in the general population, the new onset of diabetes coinciding with severe progressive neuropathy in our case suggests it is related to POEMS.

VEGF testing is a key diagnostic tool for identifying POEMS syndrome, with a cutoff of 200 pg/mL demonstrating 95% specificity and 98% sensitivity. It may

be cost-effective to test all patients with CIDP, as testing only refractory cases might be too little, too late.[7] Bone marrow aspirate and biopsy are also essential. Biopsy findings typically include megakaryocyte hyperplasia, clustering, and clonal plasma cells.[2] However, one-third of patients, particularly those with solitary or multiple solitary plasmacytomas, may have normal results.[1,2] In contrast, biopsy of bone lesions is abnormal in 90% of cases, showing diffuse infiltration of light chain-restricted plasma cells. This provides a high yield for identifying monoclonal plasma cells, especially when bone marrow biopsy results are inconclusive, as in our case.[1,2]

The use of modern therapies for POEMS, including radiation therapy, chemotherapy, and autologous stem cell transplant (ASCT), has led to relatively favorable outcomes. Ten-year survival data show a 24% improvement, with survival increasing from 55% in patients diagnosed before 2004 to 79% in those diagnosed after.[2] Neurological response is typically observed 6 months after completing therapy.

Treatment recommendations are based on bone marrow involvement. A curative response may be achieved with radiation therapy for isolated bone lesions. In patients with bone marrow involvement, systemic therapy may be recommended, with or without radiation, depending on the characteristics of the bone lesion (size and lytic component).[2] Our patient has an isolated bone lesion without clonal plasma cells on the bone marrow biopsy. In this population, targeted radiation leads to a 4-year overall survival rate of 97% and a 10-year overall survival rate of 70%, indicating a favorable prognosis.[8]

Citation

1. Keddie S, Foldes D, Caimari F, Baldeweg SE, Bomsztyk J, Ziff OJ, Fehmi J, Cerner A, Jaunmuktane Z, Brandner S, Yong K, Manji H, Carr A, Rinaldi S, Reilly MM, D'Sa S, Lunn MP. Clinical characteristics, risk factors, and outcomes of POEMS syndrome: A longitudinal cohort study. Neurology. 2020 Jul 21;95(3):e268-e279. doi: 10.1212/WNL.0000000000009940. Epub 2020 Jun 30. PMID: 32606227.
2. Dispenzieri A. POEMS syndrome: Update on diagnosis, risk-stratification, and management. Am J Hematol. 2023 Dec;98(12):1934-1950. doi: 10.1002/ajh.27081. Epub 2023 Sep 21. PMID: 37732822.
3. Mauermann ML, Sorenson EJ, Dispenzieri A, Mandrekar J, Suarez GA, Dyck PJ, Dyck PJ. Uniform demyelination and more severe axonal loss distinguish POEMS syndrome from CIDP. J Neurol Neurosurg Psychiatry. 2012 May;83(5):480-6. doi: 10.1136/jnnp-2011-301472. Epub 2012 Mar 6. PMID: 22396441.
4. Dispenzieri A, Kyle RA, Lacy MQ, Rajkumar SV, Therneau TM, Larson DR, Greipp PR, Witzig TE, Basu R, Suarez GA, Fonseca R, Lust JA, Gertz MA. POEMS syndrome: definitions and long-term outcome. Blood. 2003 Apr 1;101(7):2496-506. doi: 10.1182/blood-2002-07-2299. Epub 2002 Nov 27. PMID: 12456500.
5. Hillengass J, Usmani S, Rajkumar SV, Durie BGM, Mateos MV, Lonial S, Joao C, Anderson KC, García-Sanz R, Riva E, Du J, van de Donk N, Berdeja JG, Terpos E, Zamagni E, Kyle RA, San Miguel J, Goldschmidt H, Giralt S, Kumar S, Raje N, Ludwig H, Ocio E, Schots R, Einsele H, Schjesvold F, Chen WM, Abildgaard N, Lipe BC, Dytfeld D, Wirk BM, Drake M, Cavo M, Lahuerta JJ, Lentzsch S. International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders. Lancet Oncol. 2019 Jun;20(6):e302-e312. doi: 10.1016/S1470-2045(19)30309-2. Erratum in: Lancet Oncol. 2019 Jul;20(7):e346. doi: 10.1016/S1470-2045(19)30423-1. PMID: 31162104.
6. Li H, Huang Y, Li Y, Zheng B, Cui J, Liu M. Endocrine Manifestations in POEMS Syndrome: a case report and literature review. BMC Endocr Disord. 2019 Mar 22;19(1):33. doi: 10.1186/s12902-019-0355-6. PMID: 30902082; PMCID: PMC6431048.
7. Marsh ES, Keddie S, Terris-Prestholt F, D'Sa S, Lunn MP. Early VEGF testing in inflammatory neuropathy avoids POEMS syndrome misdiagnosis and associated costs. J Neurol Neurosurg Psychiatry. 2021 Feb;92(2):172-176. doi: 10.1136/jnnp-2020-324012. Epub 2020 Oct 26. PMID: 33106368.
8. Kourelis TV, Buadi FK, Kumar SK, Gertz MA, Lacy MQ, Dingli D, Go RS, Kapoor P, Lust JA, Hayman SR, Hwa Y, Rajkumar SV, Zeldenrust SR, Russell SJ, Lin Y, Leung N, Kyle RA, Gonsalves WI, Dispenzieri A. Long-term outcome of patients with POEMS syndrome: An update of the Mayo Clinic experience. Am J Hematol. 2016 Jun;91(6):585-9. doi: 10.1002/ajh.24356. Epub 2016 Apr 13. PMID: 26972803.