

Case Report

Beyond the acronym, POEMS syndrome, a multisystemic enigma: a case report and comprehensive evidence-based perspective

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ABSTRACT

The POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M protein and Skin changes) is a rare and complex disease involving a variety of body systems. Emphasis is placed on peripheral neuropathy and the presence of a monoclonal protein. Additionally, major and minor criteria, including bone lesions, elevated VEGF and Castleman's disease, are significant factors. On the therapeutic front, options range from radiotherapy to systemic therapy, underscoring the importance of an early treatment response. A 64-years-old diabetic male, complain with weakness in lower limbs, along with edema and hyperpigmentation. He is diagnosed with neuropathy and CIDP is confirmed in EMG. An abdominal CT scan reveals hepatomegaly. Elevated proteins are identified as a finding in the liver function tests. Subsequent serum electrophoresis confirms an increase in M protein. Treatment with bortezomib and dexamethasone is initiated, resulting in clinical improvement. Despite this progress, the patient discontinues follow-up appointments. The POEMS syndrome is a diagnostic challenge, especially when primary symptom is polyneuropathy. The main key to diagnosis is the identification of the M protein through electrophoresis and immunofixation. A multidisciplinary diagnostic remains essential in addressing its complexity.

Keywords: POEMS syndrome, Polyradiculoneuropathy, Chronic inflammatory demyelinating, Polyneuropathies

INTRODUCTION

POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein and Skin changes) is a rare multisystem disorder characterized by a monoclonal plasma cell proliferative disorder, peripheral neuropathy and osteosclerotic myeloma. Additional clinical features may include Castleman disease, elevated levels of vascular endothelial growth factor (VEGF), organomegaly, endocrine dysfunction, distinctive cutaneous manifestations and papilledema.¹ Chronic overproduction of proinflammatory cytokines contributes to microangiopathy, edema and polyneuropathy. Elevated levels of IL-1 β , TNF- α , IL-6 and VEGF secreted by plasma cells play a key role in this pathogenic process.^{2,3} Mandatory diagnostic criteria include peripheral

neuropathy (characterized by ascending paresthesias and proximal muscle weakness) along with a monoclonal lambda light-chain plasma cell disorder.^{4,5} All patients must demonstrate evidence of a monoclonal plasma cell disorder, as confirmed by serum and/or urine immunofixation (88%), bone marrow flow cytometry, or lymph node biopsy in cases of Castleman disease.⁶ The three major diagnostic criteria consist of osteosclerotic lesions (97%), elevated VEGF levels (68%) and Castleman disease (20%). Osteosclerotic lesions are predominantly detected via radiography (97%), with common involvement of the pelvis, vertebral column, ribs and proximal extremities. Notably, bone pain and pathological fractures are uncommon in these patients. Elevated VEGF serves as a valuable biomarker for monitoring therapeutic response.^{7,8} Castleman disease

arises from giant-cell lymphoid hyperplasia or angiofollicular lymphoid hyperplasia and is associated with POEMS syndrome in approximately 15% of cases.⁹ The six minor criteria comprise endocrinopathy (67%), cutaneous manifestations (68%), organomegaly (50%), fluid overload (29%), thrombocytosis/polycythemia (50%) and papilledema (29%). Among endocrine disorders, hypogonadism (70%) is the most prevalent, followed by hypothyroidism and adrenal insufficiency.

Dermatological changes include hyperpigmentation (50%) and hemangiomas (47%). Organomegaly (50%) is generally mild, primarily involving the liver, spleen and lymph nodes. Extravascular fluid accumulation (29%) may lead to ascites and peripheral edema. Hematologic abnormalities consist of polycythemia (50%) and thrombocytosis.^{10,11} The presence of unexplained peripheral neuropathy, refractory ascites or peripheral edema and gynecomastia or organomegaly of unknown etiology should raise suspicion for POEMS syndrome. The International Myeloma Working Group (IMWG) diagnostic criteria for POEMS syndrome require the coexistence of peripheral neuropathy and a monoclonal plasma cell proliferative disorder. Additionally, at least one major criterion must be met, such as osteosclerotic bone lesions, Castleman disease or elevated VEGF levels. Furthermore, at least one minor criterion is necessary, including organomegaly, extravascular fluid overload, endocrinopathy, cutaneous changes, papilledema, thrombocytosis or polycythemia.¹² The differential diagnosis includes multiple myeloma (MM), solitary plasmacytoma of bone (SPB), monoclonal gammopathy of undetermined significance (MGUS), Waldenström macroglobulinemia, primary (AL) amyloidosis and mixed cryoglobulinemia.

Unlike POEMS syndrome, these disorders are typically not associated with cutaneous manifestations. In POEMS-related chronic inflammatory demyelinating polyneuropathy (CIDP), patients exhibit greater axonal loss, reduced temporal dispersion and less pronounced conduction block compared to classical CIDP.¹³ While no standard treatment exists, patients with one to three isolated bone lesions and no evidence of bone marrow involvement should receive radiotherapy (40-50 Gy). For those with extensive osteosclerotic lesions or severe symptoms, systemic therapy similar to multiple myeloma treatment is recommended, including chemotherapy and hematopoietic cell transplantation. Initial chemotherapy may consist of melphalan-dexamethasone combinations or lenalidomide-based regimens. In eligible younger patients, high-dose melphalan followed by autologous hematopoietic cell transplantation is the preferred approach.^{14,15} Patients typically demonstrate favorable treatment responses within the first six months. Clinical monitoring should include whole-body fluorodeoxyglucose positron emission tomography (FDG-PET), VEGF level assessment and serum/urine protein electrophoresis with immunofixation. The survival rate is threefold higher than in multiple myeloma, with primary

mortality causes being cachexia and pneumonia. Median survival reaches 13.7 years in most cases.^{16,17}

CASE REPORT

A 64-year-old male with a 15-years history of type 2 diabetes, managed with metformin and adequate glycemic control (most recent HbA1c: 5.8%), presented with chronic constipation treated for one year. Four months prior to evaluation, he developed progressive lower limb weakness, fatigue, generalized asthenia, moderate exertional dyspnea and bilateral lower extremity edema (+). Two months later, he noted hyperpigmentation on his hands, prompting an evaluation for diabetic neuropathy in the internal medicine department.

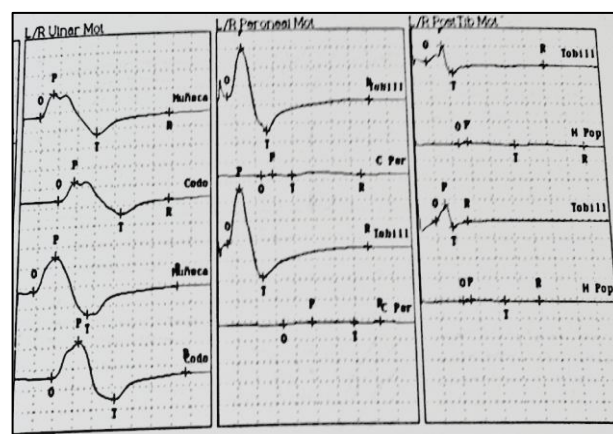


Figure 1: Polyneuropathy as clinical manifestations of POEMS Syndrome. Mixed axonal and demyelinating sensorimotor polyneuropathy, predominantly axonal, affecting median, ulnar, peroneal, tibial and sural nerves bilaterally.



Figure 2: Organomegaly as clinical manifestations of POEMS Syndrome. Abdominal CT reveals marked hepatomegaly (longitudinal 18 cm, transverse 21 cm, AP 15 cm) with homogeneous parenchyma, no biliary dilation or focal lesions.

Physical examination revealed generalized weakness, predominantly in the lower limbs (Daniels 2/5 bilaterally), along with diminished patellar and Achilles reflexes (+/++++). Electromyography findings were consistent with mixed sensorimotor polyneuropathy, exhibiting both axonal and demyelinating features, with a predominance of axonal involvement, suggestive of chronic inflammatory demyelinating polyneuropathy (CIDP) (Table 1).

Further workup included a lumbar puncture, which yielded normal results and an abdominopelvic CT scan demonstrating no intracranial lesions but revealing free abdominal fluid, chronic liver disease and hepatomegaly (longitudinal diameter: 18 cm, transverse: 21 cm, anteroposterior: 15 cm). Liver enzymes were elevated (ALT: 87 U/l (7–55), AST: 82 U/l (8–48)), alongside increased total proteins and globulins.

Urinalysis and 24-hour protein collection detected proteinuria (420 mg/24 hours). Serum protein electrophoresis identified an abnormal monoclonal band in the gamma region, later confirmed by immunofixation as an M-protein (IgG-κ, 1.8 g/dl). Due to persistent weakness, fatigue and constipation, thyroid function tests were performed, revealing hypothyroidism (TSH: 17.16 mIU/l (0.37–4.7), free T4: 0.7 ng/dl (0.8–2.7), T3: 0.5 ng/ml (0.8–2)) (Table 1).

Triyodotironina (T3) Total	0.50 ng/mL
Método : Quimioluminiscencia (CMIA)	
Tiroxina (T4) Libre	0.70 ng/dL
Método : Quimioluminiscencia	
Hormona Estimulante de Tiroides (TSH)	17.16 uIU/mL

Figure 3: Endocrinopathy as clinical manifestations of POEMS Syndrome. Findings consistent with primary hyperthyroidism (<5% of cases).

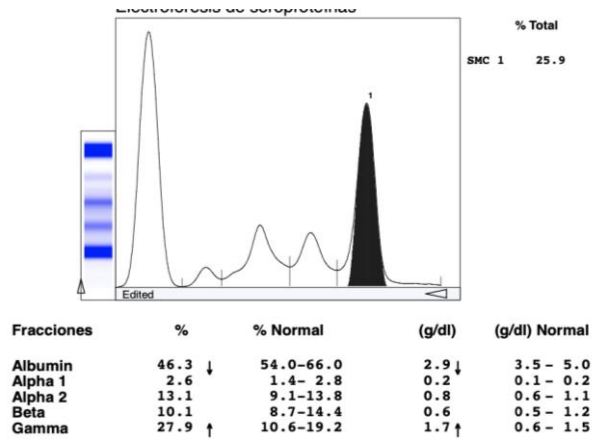


Figure 4: M protein as clinical manifestations of POEMS Syndrome. Serum protein electrophoresis shows a monoclonal spike (2.5 g/dl, gamma region). Immunofixation confirms IgG κ M-protein (1.8 g/dll).



Figure 5: Skin changes as clinical manifestations of POEMS Syndrome. Localized dermatosis on both hands' dorsum, featuring irregular hyperpigmented patches.

Table 1: Electrophysiological evidence of peripheral nerve involvement in our patient with POEMS syndrome.

Nerve evaluated	Parameter evaluated	Motor (Right)	Motor (Left)	Sensory (Right)	Sensory (Left)
Median	Amplitude (mV)	2.4	4.4	20	28
	Latency (ms)	4.5	4.2	-	-
	VCN (m/s)	34	37	-	-
Ulnar	Amplitude (mV)	3.2	3	12	15
	Latency (ms)	2.7	2.7	-	-
	VCN (m/s)	35	34	-	-
Tibial	Amplitude (mV)	3.2	1.7	-	-
	Latency (ms)	3.8	4	-	-
	VCN (m/s)	36	37	-	-
Sural	Amplitude (μV)	-	-	45	25

A skin biopsy for hyperpigmented hand lesions was declined by the patient. Based on clinical and laboratory findings, a diagnosis of POEMS syndrome was established. Hematology initiated treatment with

bortezomib (2.63 mg IV, days 1, 4, 8, 11) and dexamethasone (20 mg PO, days 1, 2, 4, 5, 8, 9, 11, 12) in 21-day cycles for six courses. The patient showed clinical improvement during hospitalization and was discharged.

However, despite outpatient follow-up and telemonitoring, he subsequently discontinued hospital visits.

DISCUSSION

POEMS syndrome is a rare and complex clinical disorder involving the nervous, endocrine and immune systems, with a wide spectrum of clinical manifestations. Chronic overproduction of proinflammatory cytokines, including IL-1 β , TNF- α and IL-6, along with VEGF, plays a key role in its pathogenesis. The condition is marked by microangiopathy, edema and subsequent polyneuropathy.

Diagnostic criteria encompass peripheral neuropathy, monoclonal plasma cell disorder and the detection of monoclonal abnormalities through serum or urine immunofixation, as well as bone marrow flow cytometry. While pathological fractures are uncommon, osteosclerotic lesions observed on radiographs are a distinctive feature of the disease. Measuring VEGF levels is valuable for assessing treatment response in affected individuals. Notably, POEMS syndrome may be associated with Castleman disease, which can occur in a subset of patients. The complexity of this disorder is further underscored by the presence of lymphoid hyperplasia, either giant or angiofollicular in nature, emphasizing the need for thorough clinical evaluation.^{18,19}

The importance of differential diagnosis lies in the similarity of symptoms with other conditions, such as multiple myeloma, diabetic neuropathy and chronic inflammatory demyelinating polyneuropathy (CIDP). A key distinguishing feature of diabetic neuropathy is its predominant involvement of sensory nerves, whereas POEMS syndrome and CIDP mainly affect motor nerves. Regarding treatment, radiotherapy may be considered for localized bone lesions, while systemic therapy is reserved for more extensive or severe cases.^{20,21}

Regarding nerve conduction studies, these help differentiate between POEMS syndrome and CIDP, as POEMS syndrome primarily exhibits demyelination in motor nerves, whereas CIDP affects both motor and sensory nerves. In POEMS syndrome, a more pronounced reduction in conduction velocities is observed, along with decreased amplitude of distal action potentials and the absence or prolongation of F-waves.²²

POEMS syndrome poses both diagnostic and therapeutic challenges, requiring a thorough understanding of its complex pathophysiology and strict adherence to diagnostic criteria. Accurate differentiation from CIDP and diabetic neuropathy is equally essential. Treatment must be tailored to each patient to optimize clinical outcomes.

CONCLUSION

This clinical case underscores the complexity and diverse manifestations associated with POEMS syndrome. The

initial diagnosis of diabetic neuropathy was challenged by symptom progression and the emergence of additional clinical features, including hyperpigmentation and hepatomegaly. Definitive diagnosis relied on the identification of M-protein through electrophoresis and subsequent immunofixation studies. The patient's clinical course during hospitalization emphasizes the necessity of a multidisciplinary approach, integrating neurological, endocrine and hematological perspectives.

Despite therapeutic intervention and outpatient follow-up, poor treatment adherence highlights the challenges in long-term management of this syndrome. Effective communication among the multidisciplinary team, along with ongoing physician education, is essential to improving patient quality of life. This case exemplifies the diagnostic and therapeutic difficulties posed by POEMS syndrome, as well as its heterogeneous clinical presentation and the need for a comprehensive management strategy. Although advances have been made in understanding and treating this condition, long-term patient adherence to follow-up and effective patient-provider communication remain critical aspects of POEMS syndrome management.

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