POEMS Syndrome Diagnosis in a Patient with Mixed Polyneuropathy: Case Report

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Abstract: POEMS syndrome is a rare condition of paraneoplasic origin characterized by the presence of a sensorimotor polyneuropathy associated with the presence of a proliferative disorder of plasmatic monoclonal cells and overproduction of vascular endothelial growth factor. The acronym "POEMS" represents multisystem findings including polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder and skin changes; nevertheless, clinical presentation is heterogeneous. We describe a clinical case, the diagnostic and therapeutic approach in a patient with sensorimotor polyneuropathy in whom POEMS syndrome was diagnosed; to understand this pathology, its clinical and paraclinical manifestations in order to make a diagnosis or to avoid a delayed one and to provide an adequate treatment.

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Introduction

POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) is a rare disease, usually related to a paraneoplastic etiology, characterized by the presence of a monoclonal plasma cell disorder, peripheral neuropathy, and increased levels of serum vascular endothelial growth factor (VEGF) (Plaza et al., 2016; Keddie et al., 2018). The acronym "POEMS" references the most frequent symptoms including: **P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal protein, and specific **S**kin changes (Plaza et al., 2016; Keddie et al., 2018). Nonetheless, clinical presentation varies greatly in each individual case, and may not present all the criteria. Suichi et al. (2019) estimated a prevalence of 0.3 for 100,000 people, however due to the rarity of said entity, this usually implies a delayed, or even subdiagnosis.

Given that POEMS syndrome is an incapacitating condition, related to high morbidity if not treated early, an opportune diagnosis is key to a more favourable prognosis and adequate lifestyle for these patients. More aggressive treatment options have been used since 2000, including high doses of chemotherapy along with autologous stem cell transplant, immunomodulators, and proteasome inhibitors (Kuwabara et al., 2012; Dispenzieri, 2017; Suichi et al., 2019). The latest evidence establishes that monoclonal antibodies against VEGF are harmful and can lead to death. This suggests that although a useful biomarker in the diagnostic stage, VEGFs pathophysiological role is poorly understood.

This syndrome is unfortunately rarely considered as a differential diagnosis among patients presenting with chronic polyneuropathy without any other related symptoms due to a generalized insufficient knowledge about said condition. This is why a better diagnostic approach plays a fundamental role in avoiding unnecessary studies and can lead to an early diagnostic approach. The objective of this article is to describe a clinical case, along with its diagnostic and therapeutic process, in a patient with mixed polyneuropathy ultimately diagnosed with POEMS syndrome.

Case report

A 47-year-old man, with a history of acute myocardial infarction with reduced left ventricular ejection fraction, who presents with 6 months of progressive distal muscle weakness that limits functionality, along with paresthesias in all four extremities, and significant weight loss. During the physical examination, generalized areflexia and hypertrophy of both lower limbs are evident.

The electromyography and nerve conduction showed a severe, predominantly demyelinating, polyneuropathy that affected both the motor and sensitive nerves in all four extremities, with a few signs of active denervation.

Other etiologies were ruled out, including deficiencies, metabolic causes, autoimmune and paraneoplastic causes (Table 1). A tomographic search for neoplastic lesions concluded mild diffuse hepatosplenomegaly and ascites. The

Table 1 – Patient laboratory results

	Laboratory tests	Value
Blood chemistry panel	hemoglobine	10 g/dl
	hematocrite	30%
	leucocytes	11,000
	platelets	332,000
	glucose	88 mg/dl
Endocrine tests	TSH	3.15 mUI/l (0.27–4.2)
	cortisol AM	10 ug/dl (100–140 mmol/l)
	ACTH	515 pg/ml (6–76 pg/ml)
Metabolic tests	proteins	6 g/dl
	albumin	3 g/dl
	B12 vitamine	653 pg/ml
	folic acid	15 ng/ml
Autoimmune tests	ANAS	1:80 diluciones
	pANCAS and cANCAS	negative
	ENAS (Ro, Sm, La, Rnp)	negative
	lupus anticoagulant	negative

TSH – thyroid-stimulating hormone; ACTH – adrenocorticotropic hormone

patient was sent home with an unsure diagnosis of a chronic, inflammatory demyelinating polyneuropathy to be treated with corticoids.

Ten months later, the patient returns with worsening paraparesis and dysesthesias, along with an exacerbation of his neurological deficit over the last 20 days, accompanied by edema of both legs (Figure 1). During the physical examination, the patient presents unresponsive hypotension, jugular engorgement, leukonychia, ascites and pitting edema of the lower limbs. Neurological findings include hypotrophy of all four extremities, strength 3/5 in upper limbs and 2/5 in lower limbs, generalized areflexia and distal multimodal hypoesthesia in lower limbs.

Considering a possible chronic polyneuropathy of unknown origin with unclear multisystemic findings, further studies were required. Due to sustained hypotension in spite of vasopressors, endocrine tests were performed which confirmed adrenal insufficiency secondary to low cortisol levels and high ACTH (adrenocorticotropic hormone) levels (Table 1). A new thoracoabdominal computed tomography (CT) showed increased hepatosplenomegaly (Figure 1).

A lumbar puncture reported an albumin-cytological dissociation which led to a sural nerve biopsy that ultimately reported an inflammatory demyelinating mixed axonal neuropathy, in addition to a serum protein electrophoresis that showed slightly elevated levels of beta-1, beta-2, and gamma. Given these findings, serum immunofixation was done which showed IgA lambda monoclonal gammopathy.

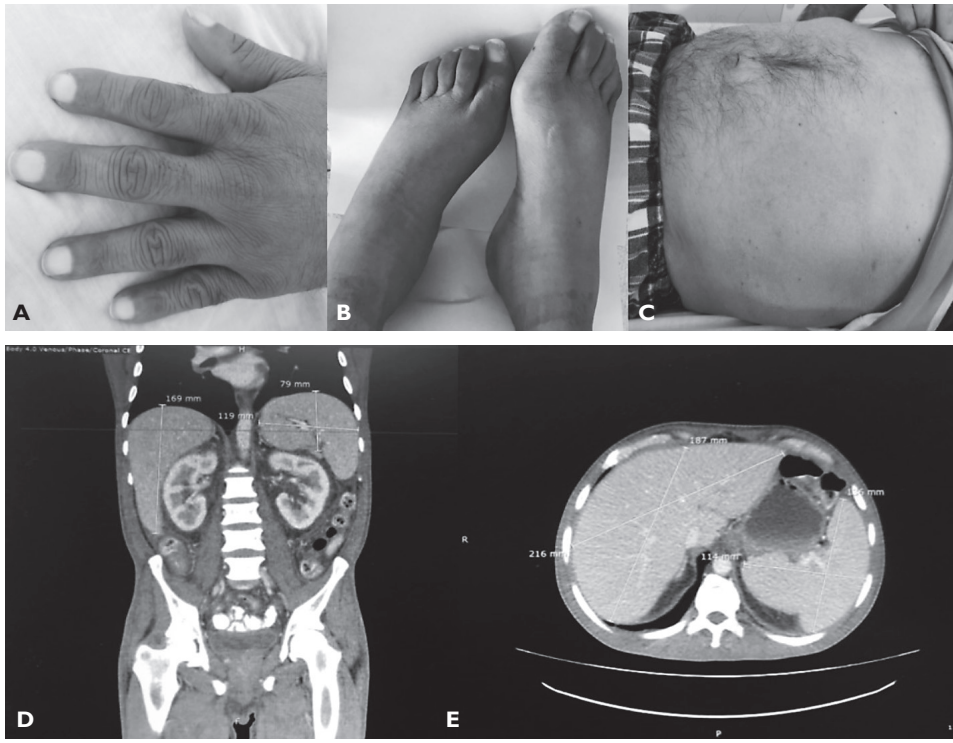

Figure 1 – Semiologic findings of the patient compatible with POEMS syndrome. A) leukonychia; B) edema; C) ascites; D) and E) hepatosplenomegaly.

Everything described previously led to a bone marrow biopsy which resulted in megakaryocytic hyperplasia, dysmegakaryopoietic changes, and increased plasmacytes.

POEMS syndrome became a more likely diagnostic possibility once two major criteria and four minor criteria (organomegaly, endocrinopathy, skin changes and volume overload) were met. Therefore, long bone X-rays were taken which ruled out the presence of lithic or sclerotic lesions. Finally, the diagnosis was confirmed thanks to a VEGF of 433.9 pg/ml (normal: 128.9 pg/ml). The patient was then referred to a level of greater complexity for a hematology consult and to decide on an autologous hematopoietic cell transplant.

Discussion

POEMS syndrome is a proliferative monoclonal plasma cell disorder that leads to a systemic inflammatory response mediated by the presence of cytokines (Gherardi et al., 1996; Michizono et al., 2001). VEGF is an angiogenic cytokine that is found significantly elevated in these cases, and therefore it is a strategic biomarker when

Table 2 – Diagnostic criteria for POEMS syndrome

Mandatory major criteria (both)	Polyneuropathy Monoclonal plasma cell-proliferative disorder
Major criteria (at least one)	Castleman's disease Sclerotic or lytic bone lesions Vascular endothelial growth factor elevation
Minor criteria (at least one)	Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) Extravascular volume overload (edema, pleural effusions, or ascites) Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid or pancreatic) Changes in skin: hypertrichosis, acrocyanosis, leukonychia Papilledema Thrombocytosis, polycythemia

making this diagnosis and during the follow-up (Watanabe et al., 1996; D'Souza et al., 2011; Keddie et al., 2018). However, the proper, official diagnosis is made using the criteria established by Dispenzieri et al. in 2003 that include clinical, paraclinical and imaging findings (Table 2).

The characteristic plasma cell disorder includes the presence monoclonal proteins, also known as paraproteins, in plasma, serum and/or urine. These are composed from a single heavy chain (M, G or A) and a single light chain (kappa or lambda). According to Vallat et al. (1996), the paraproteins usually associated to polyneuropathies tend to be IgM and kappa, which varies from a key aspect of POEMS, given that the latter tends to be associated to IgA or IgG and lambda light chains in 95% of cases, including the above-mentioned case (Vallat et al., 1996; Dispenzieri et al., 2003). In order to achieve a better test sensitivity, these proteins should be found through protein electrophoresis, immunofixation, and light chain analysis in both serum and urine samples. This should be taken in account, given that if only protein electrophoresis is done, there can be up to 30% false negatives (Dispenzieri et al., 2003).

Once confirmed, a bone marrow biopsy should be done in order to properly guide treatment. Approximately 66% of POEMS syndrome patients' biopsies will show a malignant cellular clone with a high rate of cellular abnormalities limited to expressing lambda light chains (Dispenzieri et al., 2003; Dao et al., 2011; Keddie et al., 2018). The 33% of remaining biopsies that do not show these clones could point to a cellar disorder limited to solitary or multifocal plasmacytomas located in soft or bone tissues (Dao et al., 2011; Keddie et al., 2018). It should be noted that although in the case described no malignant clones or plasmacytomas were found in the bone marrow sample, their presence cannot be completely ruled out due to their extremely small size.

Table 3 – POEMS syndrome diagnostic approach

Characteristic	Diagnostic study	Typical abnormality
Polyneuropathy	Nerve conduction/ electromyography	Axonal and demyelinating polyneuropathy, more frequent demyelinating
	Nerve biopsy	Not necessary if diagnosis is clear with elevated VEGF levels. Axonal degeneration, diffuse myelinated fiber loss, increased epineural blood vessels
	Cerebrospinal fluid*	Albuminocytologic dissociation; normal cell count; mild increase opening pressure; not specific so not always necessary
Organomegaly	CT scan of chest/abdomen/ pelvis and PET-CT	Lymph node, spleen, liver
Endocrinopathy	Adrenal: cortisol	Typically low
	Thyroid: TSH, T4	Hypothyroid or hyperthyroid
	Pituitary: LH, FSH, IGF-1, ACTH, prolactin	Typically hypofunctioning
	Gonadal: testosterone, oestradiol	Typically low
	Parathyroid: PTH	
	Pancreatic: HbA1c, glucose	Typically raised
Monoclonal plasma cell disorder	Serum protein electrophoresis Immunofixation Serum free light chain analysis	IgG or IgA lambda monoclonal protein
	Urine protein electrophoresis/ immunofixation	Bence Jones proteins
	Bone marrow biopsy ± targeted bone lesion biopsy	Presence of plasma cells in immunofixation, typically lambda light chain restricted
Skin	Clinical diagnosis	Acrocyanosis, hypertrichosis, nail changes, glomerular hemangiomas
Papilledema	Ophthalmological assessment	
Extravascular volume overload/cardiac involvement	Echocardiogram*	Reduction of let or right ventricular ejection fraction, elevation of pulmonary artery pressure; evidence of previous ischemia
Sclerotic bone lesions	CT bone windows, PET-CT imaging	Sclerotic lesions/mixed lytic with sclerotic
Thrombocytosis	Full blood count	Increased platelets
Pulmonary function	Pulmonary function tests*	Pulmonary hypertension, restrictive disease, respiratory muscle weakness, reduced diffusion capacity

*not necessary for diagnosis, but useful; VEGF – vascular endothelial growth factor; CT – computed tomography; PET – positron emission tomography; TSH – thyroid-stimulating hormone; ACTH – adrenocorticotropic hormone; LH – luteinizing hormone; PTH – parathyroid hormone; IGF-1 – insulin like growth factor-1

Due to the aforementioned, a CT or a positron emission tomography to assess the presence of lytic or bone sclerotic lesions should be taken. This is key, taking into account that a normal bone marrow biopsy could false lead to a missed or delayed diagnosis.

In what relates to the multisystemic findings, the endocrinopathy usually presents in around 65% of cases, more frequently as erectile dysfunction and gynecomastia in men, and as early menopause symptoms in women. Taking that into consideration, it is very interesting that our case presents an endocrinopathy as the adrenal insufficiency, which is a rarer disease. In regards to the organomegaly, only 50% of patients express it, and usually affecting the liver, spleen or lymphatics, as reflected in our patient's CT (Keddie et al., 2018). Lastly, multiple skin lesions have been described as frequent expression of POEMS including glomeruloid-like hemangiomas, reddish dome-shaped papules on the trunk and extremities, leukonychia and hypertrichosis (Keddie et al., 2018).

Though rare, it is a diagnosis that should be considered in patients with chronic, usually demyelinating, polyneuropathy of unclear origin who also present multisystemic findings. One of its main differential diagnosis is Demyelinating Chronic Inflammatory Polyneuropathy. Up to 60% of POEMS patients are initially diagnosed with said pathology, wrongly treated with immunomodulatory therapy, which would result ineffective and essentially just delay the actual diagnosis for a period of around 12 months (Nasu et al., 2012). Table 3 exhibits the diagnostic tools for a proper approach to POEMS syndrome.

As far as for treatment for POEMS, the use of monoclonal antibodies that block VEGF has been proved to be harmful to the patient, even fatal, which just goes to show that although a useful diagnostic biomarker, VEGF's pathophysiological role is still unclear (Keddie et al., 2018). The main therapeutic goal is to suppress monoclonal plasma cell proliferation. In cases with systemic affection (bone marrow, or 3 or more plasmacytomas), gold standard treatment includes autologous stem cell transplant and chemotherapy. In patients with localized affection (less than 2 plasmacytomas without bone marrow affectation) radiotherapy is recommended (Dispenzieri, 2017; Keddie et al., 2018).

We depicted a clinical case describing a patient with POEMS syndrome, which was diagnosed taking into account the expression of multisystemic findings along with his chronic neuropathy. This report highlights the significance of an adequate semiological evaluation and high diagnostic suspicion to achieve a timely detection of this pathology, looking to avoid clinical progression and unnecessary studies. In closing, opportune treatment plays a fundamental role in avoiding clinical deterioration, therefore emphasizing the importance of considering POEMS syndrome a differential diagnosis in patients presenting with chronic polyneuropathy and Demyelinating Chronic Inflammatory Polyneuropathy accompanied by other seemingly unrelated findings.

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