

Case Report

POEMS syndrome: challenges in the diagnosis of an atypical case

Síndrome POEMS: desafios no diagnóstico de um caso atípico

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ABSTRACT: *Introduction:* POEMS syndrome is a rare paraneoplastic event, with no current report in the literature about its real prevalence. Most cases occur in middle-aged men. *Case Report:* Male patient, 65 years old, complaining of edema and paresthesia in the legs that evolved to plegia, associated with hyporexia and fatigue. Initial outpatient investigation revealed Chronic Inflammatory Demyelination Polyradiculoneuropathy (CIDP) of undefined etiology. Excluding secondary symptoms, the patient was diagnosed with primary hypothyroidism, severe hypogonadism, hyperic skin lesions, ascites, pleural effusion and thrombocytosis, in addition to monoclonal IgA Lambda gammopathy by serum immunofixation test. Viral serologies were negative. Excluding the possibility of Multiple Myeloma and other gammopathies, the hypothesis of POEMS Syndrome was proposed, and plasma VEGF measurement was performed (425 pg/mL; RV = <96.2). This is an atypical case, as bone lesions, present in up to 97% of cases, were not found in the patient in question, making the diagnosis challenging. *Conclusions:* The diagnosis of rare syndromes, although challenging, allows a broader view of the patient, as it increases clinical reasoning.

Keywords: POEMS syndrome; Differential diagnosis; Paraproteinemias; Paraneoplastic polyneuropathy; Diseases of endocrine system.

RESUMO: *Introdução:* Síndrome POEMS trata de um raro evento paraneoplásico, sem relato atual na literatura sobre sua real prevalência. A maior parte dos casos ocorre em homens de meia idade. *Relato do Caso:* Paciente masculino, 65 anos, com queixa edema e parestesia em pernas que evoluiu para plegia, associada a hiporexia e fadiga. Investigação ambulatorial inicial evidenciou Polirradiculoneuropatia Inflamatória Desmielinizante Crônica (PIDC) de etiologia indefinida. Excluídos secundarismos, o paciente foi diagnosticado com hipotireoidismo primário, hipogonadismo severo, lesões hipericrômicas em pele, ascite, derrame pleural e trombocitose, além de gamopatia monoclonal IgA Lambda por imunofixação sérica. Sorologias virais negativas. Excluída a possibilidade de Mieloma Múltiplo e outras gamopatias, foi aventada a hipótese de Síndrome POEMS, sendo realizada dosagem de VEGF plasmática (425 pg/mL; VR = <96.2). Trata-se de um caso atípico na medida em que, lesões ósseas, presentes em até 97% dos casos, não foram evidenciadas no paciente em questão, tornando desafiador o diagnóstico. *Conclusões:* O diagnóstico de síndromes raras, embora desafiante, traz ao clínico um olhar mais amplo do paciente na medida em que incrementa o raciocínio clínico.

Palavras-chave: Síndrome POEMS; Diagnóstico diferencial; Paraproteinemias; Polineuropatia paraneoplásica; Doenças do sistema endócrino.

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INTRODUCTION

POEMS syndrome was first reported in 1956, when an association of peripheral polyneuropathy, plasma cell dyscrasia, and skin disease was described. However, only in 1980, did Bardwick et al.¹ suggest the acronym “POEMS” to refer to a syndrome that involved: polyneuropathy, organomegaly, endocrinopathy, M-proteins, and skin changes.

The POEMS syndrome is a rare multisystemic paraneoplastic pathology of plasma cells. There are no current data in the literature on its real prevalence, due to the scarcity of reports. This syndrome is also known as osteosclerotic myeloma, crow-fukase syndrome, and Takatsuki syndrome. Most cases occur in middle-aged men¹.

To date, POEMS syndrome has an unknown etiology. Although many of the manifestations of multiple myeloma are directly related to the monoclonal immunoglobulin deposition, in POEMS syndrome, a derived condition, this correlation has not been found in the histopathological studies of the affected organs and nerves². However, the increased production of cytokines such as IL-1 β , IL-6, TNF- α and vascular endothelial growth factor (VEGF) seems to play an important role in the pathogenesis of the disease³.

The diagnostic criteria were updated in 2019, and the diagnosis is currently based on a system of criteria. Nowadays, two mandatory criteria, at least one of three major criteria, and one of 6 minor criteria must be present to confirm a diagnosis. The mandatory criteria are polyradiculoneuropathy (typically demyelinating) and elevated monoclonal protein. The major criteria are sclerotic bone lesions, elevated VEGF⁴ and the presence of Castleman disease (rare neoplastic lymphoproliferative disorder of the polyclonal lymph nodes). Minor criteria include organomegaly, endocrinopathy, characteristic skin changes, papilledema, extravascular volume overload, and thrombocytosis^{5,6}. With only one criterion of each class, the diagnosis will be confirmed. It is important to emphasize that other findings may be part of the disease, but not of the final diagnosis.

Neuropathy is usually the predominant feature and the first manifestation of the disease. In these cases, it presents as progressive ascending symmetrical sensorimotor impairments on extremities. Symptoms usually start in the feet, with paresthesia and coldness, followed by the motor symptoms of incoordination and muscle weakness, which dominate the neurological picture^{7,8}. Electromyography reveals slowing of nerve conduction, prolonged distal latencies, and attenuation of compound muscle action potentials¹².

At least two-thirds of patients with POEMS syndrome have one or more of the following endocrine

abnormalities, detected through clinical or laboratory evaluation: hypogonadism, hypothyroidism, diabetes mellitus, adrenal insufficiency, or hypoparathyroidism. hypogonadism is the most common endocrine abnormality and about 70% of male patients had erectile dysfunction or low testosterone levels at diagnosis^{7,8}.

Sclerotic bone lesions can be detected by conventional radiography in up to 97% of patients, even though it is not a mandatory criterion for the diagnosis of the syndrome. The patient of this report differs from the others in this aspect, as additional investigation did not reveal any kind of bone lesion.

As the pathogenesis of the syndrome is not well understood, risk stratification is limited to clinical phenotype rather than specific molecular markers. The number of clinical criteria is not prognostic, but the extent of the plasma cell disorder is. Patients who do not reveal a plasma cell clone are candidates for local radiotherapy, and those with a more disseminated clone are candidates for systemic therapy^{7,9}.

METHODS

This study was submitted to the Research Ethics Committee of the proposing *Real Hospital Português* in Recife/PE with the consent form signed by the patients and other documents from the institution and from the researchers and was approved under CAAE: 51997321.3.0000.9030 – Opinion n^o: 5,069,800. This is a descriptive case report study, in which the researchers search, record, analyze, classify, interpret and confront the facts or phenomena (variables), without interfering with or manipulating them, with subsequent literature review comparing the study data with those found in research.

CASE REPORT

JMS, 65 years old, previously healthy, with no comorbidities and not on long-term use of daily medication, was admitted to the Clinical Medicine Unit reporting that 6 months before admission he had started to experience edema and paresthesia in lower extremities (LE), mainly in the legs, which progressed to paraplegia associated with weight loss and fatigue.

Symptomatic Assessment showed general and constitutional symptoms of fatigue, asthenia, hyporexia, and unspecified weight loss. He reported the presence of hyperchromic macules, mainly in the cephalic pole (Figure 1), and hypochromic and achromic lesions in the lower extremity (Figure 2). He also complained of lower extremity edema associated with loss of motor strength and paresthesia. SA was negative in the other systems. The patient denied fever and cough.



Source: Study data

Figure 1 – Hyperchromic lesions in the cephalic pole observed on physical examination



Source: Study data

Figure 2 – Achromic/Hypochromic Lesions in lower extremities observed on physical examination

As for personal history, the patient denied smoking and reported social drinking, which he had stopped 10 years before. He denied allergies, transfusions, and previous hospitalizations. As for the surgical history of the patient, he reported a cataract surgery in 2002. The patient had positive epidemiology for schistosomiasis and positive family history of systemic arterial hypertension and diabetes mellitus.

Physical examination at admission did not reveal significant findings, except for those already mentioned in

the SA and mild hepatomegaly, also evidenced by imaging methods. The patient had started an outpatient evaluation of the condition by performing an electroneuromyography, which showed chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) of unknown etiology.

Secondary systemic conditions associated with CIDP such as hepatitis B and C, nephrotic syndrome, HIV, lupus, and inflammatory bowel diseases were excluded through clinical and laboratory screening. Magnetic resonance imaging of the lumbosacral spine and skull was also performed, but did not show any relevant findings that could justify the condition. General laboratory tests showed mild normocytic/normochromic anemia, normal iron kinetics, and normal levels of vitamins B12 and folate, so a hypothesis of anemia of chronic disease and atypical peripheral plasmacytosis (fluctuating between 8 and 9%) was proposed. Biochemistry profile, electrolytes, and liver and kidney functions were normal.

During hospitalization, thyroid function tests were requested to evaluate the condition. The tests showed Free T4 = 0.34ng/ dL and TSH = 9.56mU/L, revealing primary hypothyroidism. However, tests of autoimmunity were negative (Anti-TPO and Anti-TBG negative). Thyroid ultrasound showed no abnormalities. Total and Free Testosterone were also measured, with values of 16ng/ dL and 0.18ng/dL respectively (Reference Range = 86.49 – 788.22 and 1.9 – 19.0), leading to the hypothesis of hypogonadism, probably of central etiology, considering that Follicle Stimulating hormones (FSH) and Luteinizing hormones (LH) were inappropriately normal. There was not enough time for a drug feedback test, so an initial hypothesis of central hypogonadotropic hypogonadism was proposed. Prolactin was normal; antinuclear factor and rheumatoid factor were also measured and were non-reactive. In the evaluation of hypogonadism, nuclear magnetic resonance scans of the sella turcica showed a pituitary microadenoma of 0.6cm x 0.6cm, with a deviation of the pituitary stalk to the left and slight depression of the sellar floor, of undefined etiology until then, so it was initially considered by the team as an incidentaloma.

In the evaluation of lower extremity edema, measurements of total proteins and fractions showed mild hypoalbuminemia associated with a slight increase in serum globulins. Transthoracic echocardiogram showed no changes. Lower extremity Doppler ultrasound did not show thrombotic processes that could explain the condition.

In this context, as the patient showed peripheral demyelinating polyradiculoneuropathy, anemia, organomegaly, and endocrinopathies, the hypothesis of associated monoclonal gammopathy was proposed and additional tests were requested: serum protein electrophoresis, serum immunofixation, myelogram, cerebrospinal fluid collection, radiographs of long bones and skull, partial urine and 24h proteinuria.

Serum protein electrophoresis showed an increase

in globulin fractions, and immunofixation isolated IgA Lambda monoclonal proteins in serum. The myelogram performed was nonspecific, showing megakaryocytic hyperplasia, with mildly exacerbated thrombocytopenia and 8% of plasma cells. CSF showed significantly increased protein level (435mg/ dL with Reference Range up to 40mg/ dL) and a positive Pandy test. Other parameters were unaltered.

The radiographs of long bones and skull did not show lytic lesions suggestive of Multiple Myeloma. Urinalysis also showed no significant changes. From then on, with new findings confirming monoclonal gammopathy, the possibility of POEMS Syndrome was raised, as the patient started to present the two mandatory criteria for a definitive diagnosis. As there were already other minor criteria, including the skin changes shown in Figures 1 and 2, only one of the three major criteria was still necessary for a diagnosis, according to the most recent guidelines.

The first major criterion, osteolytic lesions, which can be seen in up to 97% of cases, was not present in our patient. Despite extensive investigations with radiographs and CT scans, no lesions were found. The other major criteria, Castleman Disease and elevated Vascular Endothelial Growth Factor (VEGF), were investigated.

Plasma VEGF levels were 425pg/ mL, and the acceptable reference range goes up to 96.2pg/ mL. Thus, the patient presented all the formal criteria and was diagnosed with POEMS Syndrome with atypical presentation – without osteolytic lesions.

DISCUSSION

POEMS syndrome describes a set of findings in patients with plasma cell dyscrasia. It is a multisystemic paraneoplastic syndrome that is morbid for those affected.

It is known that this syndrome can occur in parallel with Myeloma, so much so that it is also known by the term “Osteosclerotic Myeloma”. However, despite the fact that up to 97% of the POEMS syndrome cases present with osteolytic lesions⁵, this was not the case with our patient. Therefore, his case was even rarer, as he showed an atypical presentation of an already uncommon syndrome⁶. In a Chinese study that evaluated 1946 cases of POEMS syndrome, VEGF level was used as diagnostic criteria in only 29 patients, which makes this case even more particular, as this measurement would be the only

other possible diagnostic criterion¹¹.

When evaluating a patient with demyelinating neuropathy, it is important to think about associated differential diagnoses such as monoclonal gammopathies. In the case described, the initial investigation pointed to CIDP of undefined etiology, and only later that the presence of monoclonal Lambda light chain proteins in serum was discovered (the most common found in patients with POEMS syndrome)^{5,6}.

Based on the association between demyelinating neuropathy and monoclonal gammopathy, which are the mandatory criteria, there must be only one major criterion and one minor criterion for diagnostic confirmation. Most of the times, the major criterion associated is the presence of bone lesion, which was not found in our patient, and was the reason why plasma VEGF measurement was necessary – an expensive and inaccessible test, which had to be conducted in the United States, as it was unavailable in the national territory at the time of the patient’s clinical investigation.

After the diagnosis, the patient (who was already presenting with hemiplegia on admission) was transferred to a center with expertise and experience in the treatment of patients with POEMS Syndrome in São Paulo. However, the patient ended up dying from complications of the disease before the proposed treatment – Bone Marrow Transplantation – could be implemented.

CONCLUSION

We report a rare case of POEMS syndrome, with no osteolytic lesions (seen in up to 97% of cases), whose most important initial differential diagnosis was chronic inflammatory demyelinating polyneuropathy. The distinction between the two diseases is essential for the proper choice of treatment.

The diagnosis of POEMS is challenging and often late, as it is a rare plasma cell dyscrasia, with an indolent course and variable survival. It should be a hypothesis in patients with chronic inflammatory demyelinating polyneuropathy who have an evident monoclonal protein and/or those who do not respond to the usual initial treatment.

Thus, it is understood that early diagnosis, supportive care, and targeted therapy against plasma cells result in a better prognosis for the patient in most cases.

Study setting: Study carried out by the Clinical Medicine Unit of the Hospital Santa Casa de Misericórdia de Recife/PE

Study approved by the Research Ethics Committee of the Real Hospital Português in Recife/PE – CAAE: 51997321.3.0000.9030 – Opinion No: 5.069.800.

Sent in Attachment: Opinion of the CEP and signed TCLE .

Conflicts of interest: The authors DENY.

Study presented as a Banner at the 16th Brazilian Congress of Clinical Medicine (Oct. 08-11, 2021 – Campinas, SP).

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REFERENCES

- 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 (Baltimore)*. 1980;59(4):311-22. doi: <https://doi.org/10.1097/00005792-198007000-00006>
- Bergouignan FX, Massonnat R, Vital C, Barat M, Henry P, Leng B, Effroy C. Uncompacted lamellae in three patients with POEMS syndrome. *Eur Neurol*. 1987;27:173-81. doi: <https://doi.org/10.1159/000116152>
- Gherardi RK, Bélec L, Soubrier M, Malapert D, Zuber M, Viard JP, Intrator L, Degos JD, Authier FJ. Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome. *Blood*. 1996;87:1458-65. <https://doi.org/10.1182/blood.V87.4.1458.bloodjournal8741458>
- Hashiguchi T, Arimura K, Matsumuro K, Otsuka R, Watanabe O, Jonosono M, Maruyama Y, Maruyama I, Osame M. Highly concentrated vascular endothelial growth factor in platelets in Crow-Fukase syndrome. *Muscle Nerve*. 2000;23(7):1051-6. doi: [https://doi.org/10.1002/1097-4598\(200007\)23:7<1051::aid-mus7>3.0.co;2-v](https://doi.org/10.1002/1097-4598(200007)23:7<1051::aid-mus7>3.0.co;2-v)
- Dispenzieri A. POEMS syndrome: 2019 Update on diagnosis, risk stratification, and management. *Am J Hematol*. 2019;94:812-827. doi: <https://doi.org/10.1002/ajh.25495>
- Pinto Neto JV. Síndrome de POEMS (mieloma osteoesclerótico). *Rev Bras Hematol Hemoter*. 2007;29(1):98-102. <https://doi.org/10.1590/S1516-84842007000100018>
- Bulisanil ACP, Bueno LSM, Barros e Silva MJ, Giordani E, Guimarães HP, Lopes RD, Lopes AC. Síndrome de POEMS (polineuropatia, organomegalia, endocrinopatia, proteína M e alterações da pele). Relato de caso. *Rev Bras Clin Med*. 2008;6:202-4. Disponível em: <http://files.bvs.br/upload/S/1679-1010/2008/v6n5/a202-204.pdf>
- 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;101:2496. doi: <https://doi.org/10.1182/blood-2002-07-2299>
- Jaccard A, Royer B, Bordessoule D, Brouet JC, Femand JP. High-dose therapy and autologous blood stem cell transplantation in POEMS syndrome. *Blood*. 2002;99:3057-9. doi: <https://doi.org/10.1182/blood.v99.8.3057>
- Jurczyszyn A, Castillo JJ, Olszewska-Szopa M, Kumar L, Thibaud S, Richter J, Flicker K, Fiala M, Vij R, Yi S, Xu F, Silbermann R, Gaisan CM, Ocio EM, Waszczuk-Gajda A, Crusoe EQ, Salomon-Perzyński A, Hus I, Valls JD, Gozzetti A, Czepiel J, Krzanowska K, Chappell A, Chellapuram SK, Suska A. POEMS syndrome: real world experience in diagnosis and systemic therapy – 108 patients multicenter analysis. *Clin Lymphoma Myeloma Leuk*. 2021;22(5):297-304 doi: <https://doi.org/10.1016/j.clml.2021.10.007>
- Wang Y, Huang L-B, Shi Y-H, Fu H, Xu Z, Zheng G-Q, Wang Y. Characteristics of 1946 Cases of POEMS syndrome in Chinese subjects: a literature-based study. *Front Immunol*. 2019;10:1428. doi: <https://doi.org/10.3389/fimmu.2019.01428>
- Min JH, Hong YH, Lee KW. Electrophysiological features of patients with POEMS syndrome. *Clin Neurophysiol*. 2005;116(4):965-968. doi: <https://doi.org/10.1016/j.clinph.2004.11.011>

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