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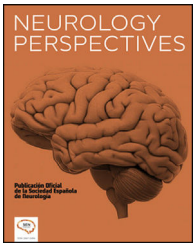

ORIGINAL ARTICLE

POEMS syndrome in Colombia: Clinical findings, therapeutic options and outcomes in a case series

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KEYWORDS
POEMS syndrome;
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Plasmacytoma;
Castleman's disease

Abstract
Introduction: POEMS syndrome is a paraneoplastic syndrome associated with a clonal plasma cell neoplasm, in general is a rare disease and its descriptions are based on series and case reports.
Objective: To describe the clinical features and outcomes in a case series of patients with POEMS syndrome.
Material and methods: Patients who met the diagnostic criteria for POEMS syndrome proposed by Dispenzieri were selected. These patients came from the medical consultation of different neurologists specialized in neuromuscular pathology in the period from 2005 to 2021; likewise, a review of the Colombian literature of all published cases of patients with diagnosis of POEMS syndrome was performed. As a result, 16 cases of patients with this diagnosis were collected and reviewed.
Discussion and conclusion: The symptoms, clinical course and treatment of our case series are similar to those published in the global literature. Early diagnosis and active treatment significantly modify the progression of the disease, as well as its overall prognosis. Patients with longer survival and lower disease burden were those who received adjuvant treatment with autologous stem cell transplantation.

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PALABRAS CLAVE
Síndrome POEMS;
Polineuropatía;
Paraneoplásico;
Plasmocitoma;
Enfermedad de Castleman

El síndrome POEMS en Colombia: allazgos clínicos, opciones terapéuticas y resultados de una serie de casos

Resumen
Introducción: El síndrome POEMS es un trastorno paraneoplásico relacionado con una neoplasia clonal de células plasmáticas. La evidencia disponible sobre esta enfermedad rara proviene de estudios de casos y series de casos.
Objetivo: Nuestro objetivo es describir las características clínicas y los resultados de una serie de casos de síndrome POEMS.
Materiales y método: Seleccionamos pacientes que cumplían con los criterios diagnósticos de síndrome POEMS propuestos por Dispenzieri. Dichos pacientes fueron atendidos en las consultas de neurólogos especializados en patología neuromuscular entre 2005 y 2021. También realizamos una revisión de la literatura que incluyó todos los casos de pacientes con síndrome POEMS diagnosticados en Colombia. La muestra final incluyó 16 pacientes con dicho diagnóstico, cuyos resultados revisamos.
Discusión y conclusión: Los síntomas, el curso clínico y el tratamiento en nuestra serie de casos fueron similares a los descritos en la literatura internacional. El diagnóstico precoz y un tratamiento activo logran modificar significativamente el avance de la enfermedad y el pronóstico de los pacientes. Aquellos pacientes sometidos a trasplante autólogo de células madre como tratamiento complementario mostraron una supervivencia mayor y una menor carga de la enfermedad.

Introduction

POEMS syndrome, identified by its acronyms P: polyneuropathy, O: organomegaly, E: endocrinopathy, M: M protein, S: skin changes (see Fig. 1); is a paraneoplastic syndrome due to an underlying plasma cell neoplasm. The diagnosis of this entity is often delayed because the syndrome is rare and can be confused with other neurological disorders, most commonly with a chronic inflammatory demyelinating polyradiculoneuropathy.[1]

The first descriptions of this entity date back to 1938 by Scheinker. In 1980, the name POEMS was attached by Bardwick and later the understanding of this entity was expanded especially by the contributions of Dispenzieri.[1,2] It has also been called Crow-Fukase syndrome, osteosclerotic myeloma, or Takatsuki syndrome.[3]

POEMS syndrome has a variable demographic distribution, the largest case series being from Japan, the United States, France, China, and India. In Japan, it has a prevalence of 0.3 cases per 100 000 population per year.[4]

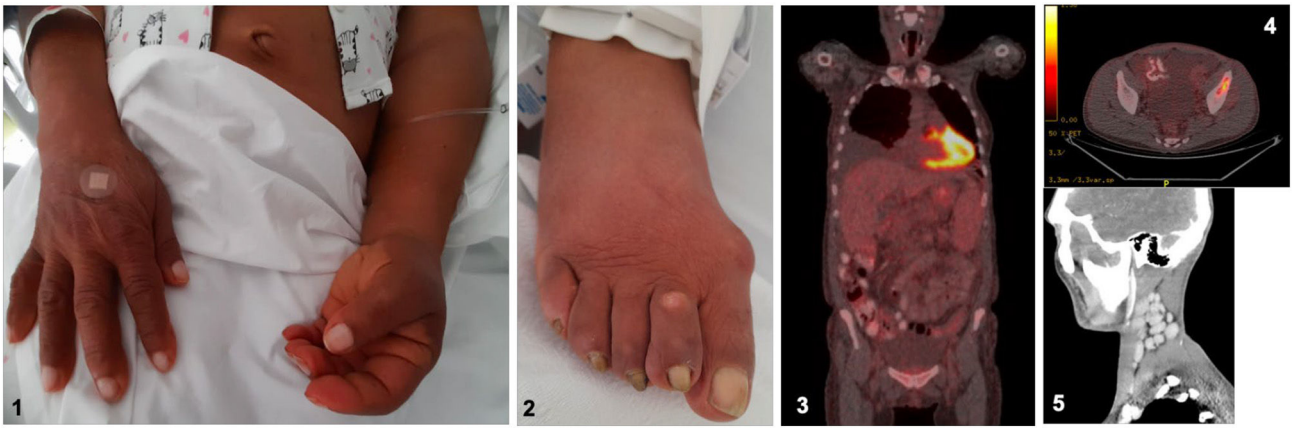

Fig. 1 General findings in patients with POEMS syndrome. Panel 1 and 2. Patient with hyperpigmentation and skin thickening. Acrocyanosis in the extremities, edema, and ascites. Panel 3 and 4. Body FDG PET-CT: no unusual metabolic changes are observed but she has hepato-splenomegaly. Body FDG PET-CT: hypermetabolic lesion in left iliac crest, later characterized by biopsy as a plasmacytoma. Panel 5. CT scan of the neck showing a cervical lymph node conglomerate.

There are some important points that relate to the acronym of this syndrome and is that not all features within the acronym are required to make the diagnosis; likewise, there are other important features not included in the POEMS acronym, which include: papilledema, extravascular volume overload, sclerotic bone lesions, thrombocytosis/ erythrocytosis, elevated levels of vascular endothelial growth factor (VEGF), a predisposition to thrombosis, and abnormal pulmonary function tests.[1,4]

Its pathogenesis is not entirely clear, however, in recent years, VEGF has been proposed as central to the pathogenesis of this entity. Plasma cells exert inflammatory mechanisms explain the systemic involvement of this entity, especially mediated by cytokines (e.g., IL-6), procoagulant and inflammatory endothelial states, platelet aggregation, and tissue ischemia.[4]

Regarding the diagnostic criteria proposed by Dispenzieri, these criteria are divided into mandatory, major, and minor criteria. To make the diagnosis of POEMS syndrome at least 1 major and 1 minor criterion is required, always in relation to the mandatory criteria, which are the presence of neuropathy and M protein. The minor criteria are: organomegaly, endocrinopathies, volume overload and extravasation, dermatologic changes, papilledema, thrombocytosis, and polycythemia.[1]

Materials and methods

Patients who met the diagnostic criteria for POEMS syndrome proposed by Dispenzieri in 2003 during the period from 2005 to 2021 in the medical consultation of different neurologists specialized in neuromuscular pathology were selected. Also, a review of all published cases of POEMS syndrome in Colombian literature were included. For the analysis we included demographic features, signs, and symptoms, findings in diagnostic studies, general complications, treatment, and follow-up time to assess survival.

Results

As a result, 16 patients diagnosed with POEMS syndrome were obtained (5–9). The criteria proposed by Dispenzieri were applied and their diagnosis was verified. Of the 16 patients selected from 2005 to 2021, the mean age was 49.5 years (range 37–67 years) and the sex ratio was 7 males and 9 females. We found that 100% of all patients had a polyneuropathy documented by electrodiagnosis, at least 75% of patients had a demyelinating pattern, and there were also predominantly axonal polyneuropathies in 3 cases; however, several of the cases reported in the literature do not detail the characteristics of the polyneuropathy (*see* Table 1).

The 100% of patients had organomegaly, of them 81.2% hepatomegaly, 43.7% splenomegaly, and 56.2% lymphadenopathy. Endocrinopathies was present in 100% of the patients, the most frequent finding of endocrinopathies was hypothyroidism (81.2%), followed by sexual impotence (31.2%), diabetes mellitus (31.2%), hyperprolactinemia (25%), hyperparathyroidism (12.5%), and finally hypoparathyroidism (6.2%).

Table 1 Demographic, clinical and electrophysiological characteristics, findings in complementary studies.

Characteristics of patients with POEMS Syndrome
Number of patients (n): 16
Demographic characteristics

- **Sex:** 9 women and 7 men
- **Age:** between 37–67 (49.5)

Polyneuropathy (16/16) - 100%

- Motor and sensory demyelinating (9/13)
- Motor demyelinating (1/13)
- Axonal sensory motor (3/13)

Plasmocitoma (4/16) – 25%
Castleman disease (5/16) – 31.2%
Organomegaly (16/16) - 100%

- Hepatomegaly (13/16) - 81.2%.
- Splenomegaly (7/16) - 43.7%
- Lymphadenopathy (9/16) - 56.2%

Endocrinopathy (16/16) - 100%

- Hypothyroidism (13/16) - 81.2%.
- Diabetes mellitus (5/16) - 31.2%
- Hyperparathyroidism (2/16) - 12.5%
- Hypoparathyroidism (1/16) - 6.2%
- Hyperprolactinemia (4/16) - 25%
- Impotence (5/16) - 31.2%
- Hypogonadism (5/16) - 31.2%

M protein (16/16) - 100%

- IgA lambda (6/16) – 37.5%
- IgG lambda (5/16) – 31.2%
- IgM lambda (2/16) –12.5%
- IgM Kappa (2/16) – 12.5%
- IgG Kappa (3/16) – 18.7%

Skin changes (16/16) – 100%

- Hyperpigmentation (16/16) - 100%
- Acrocyanosis (3/16) - 18.7%
- Telangiectasia (1/16) - 6.25%
- Hypertrichosis (3/16) - 18.7%
- Thickening (9/16) - 56.2%
- Acropachy (2/16) - 12.5%
- Leukonychia (5/16) - 31.2%
- Others (5/16) - 31.2%

Edema (13/16) - 81.2%

- Peripheral edema (13/16) - 81.2%.
- Ascites (10/16) - 62.5%
- Pleural effusion (7/16) - 43.7%
- Pericardial effusion (5/16) - 31.2%
- Papilledema (7/16) - 43.7%

Other characteristics

- Bone lesions (8/16) - 50%.
- Thrombocytosis (3/16) - 18.7%
- Polycythemia (1/16) - 6.2%
- Pulmonary hypertension (7/16) - 43.7%
- Weight loss (15/16) - 43.7%
- Weight loss (15/16) - 93.7%
- Fatigue (12/16) - 93.7%
- Elevation of VEGF (6/10) - 60%

Concerning to monoclonal plasma proliferative disorders, 100% had documented detection of serum immunofixation, 37.5% had abnormal immunoglobulin A (IgA) lambda, 31.2% had IgG lambda, and 12.5% IgM lambda. 18.7% had elevated IgG and 13.3% had IgM Kappa. There were no patients with negative serum immunofixation.

The dermatologic findings were seen in 100%, the most frequent abnormality was hyperpigmentation (100%), followed by thickening (56.2%), leukonychia (31.2%), hypertrichosis (18.7%), acrocyanosis (18.7%), and acropaquia (12.5%). 5 patients had rare dermatologic manifestations.

Edema was found in 100% of patients, they had signs of fluid overload, the main one being peripheral edema (81.2%), followed by ascites (62.5%), pleural effusion (43.7%), papilledema (43.7%), and pericardial effusion (31.2%).

Less frequent, findings included thrombocytosis (18.7%), polycythemia (6.2%), and 1 patient had concomitant indolent multiple myeloma. Within systemic symptoms, 93.7% of patients reported weight loss and 75% asthenia. Only 50% had bone lesions and VEGF elevation was seen in 60%.

In addition, 93.75% of patients received targeted treatments for the disease, which included chemotherapeutics, alkylating agents, steroids, and autologous stem cell transplantation. 87.5% received steroids, 37.5% Cyclophosphamide, 37.5% Melphalan, and 31.2% with MCT. In lower frequency Lenalidomide, Bortezomib, radiotherapy and Thalidomide (*see* Table 2).

Follow-up was documented in 9 patients, and this was on average 1–18 years (median 4 years). During follow-up 3 patients died from different causes, especially cardiovascular and infectious complications.

Table 2 Complications, treatment and follow-up.

Complications (5/16)

- Heart failure (4/16) - 25%.
- Cardiomyopathy (1/16) - 6.2%
- Cerebrovascular complication (1/16) - 6.2%

Treatment (16/16)

- Radiotherapy (1/16) - 6.2%
- Corticosteroids (14/16) - 87.5%
- Melphalan (6/16) - 37.5%
- ASCT (5/16) - 31.2%
- Thalidomide (1/16) - 6.2%
- Lenalidomide (2/16) - 12.5%
- Bortezomib (2/16) - 12.5%
- Cyclophosphamide (6/16) - 37.5%

Survival

- Follow-up time: 1–18 years in 9 patients (median 4 years).
- Mortality during follow-up: 3/9 patients

ASCT: autologous stem cell transplant

Discussion

This study reviewed the clinical characteristics of 16 patients diagnosed with POEMS syndrome in Colombia. Clinical manifestations were diverse, including motor symptoms, sensory symptoms, constitutional symptoms, adenopathy, signs of water overload, and cutaneous hyperpigmentation. Imaging studies and laboratory tests also showed hepatomegaly, splenomegaly, thrombocytosis, endocrinopathies, and positive serum immunofixation in most patients. In addition, increased plasma cells in the bone marrow, Castleman's disease, and plasmacytoma, in one of them plasmacytoma and multiple myeloma with indolent course coexisted. Interestingly, the percentage of patients with polycythemia and thrombocytosis in our case series was much lower compared to what has been published.

All follow-up patients were treated with combination chemotherapy based on alkylating agents or corticosteroids, cyclophosphamide, thalidomide, lenalidomide with or without autologous stem cell transplantation. Unfortunately, 3 patients died during follow-up in the first 3–4 years after diagnosis of POEMS syndrome, mainly due to cardiovascular and infectious complications. One of the patients had an ischemic stroke of cryptogenic etiology, being one of the complications associated with POEMS syndrome that is not contemplated within the diagnostic criteria.

Patients showed a well treatment response, but not complete remission. Furthermore, those who showed greater remission and survival were those who received adjuvant therapy with autologous stem cell transplantation, a finding that is identified as one of the therapeutic options that has the greatest impact on the natural course of the disease when systemic involvement exists.[1,10] The results presented in this cohort of patients with POEMS syndrome are consistent with the larger case series published by *Bardwick, Takatsuki, Nakanishi, Soubrier, Lin, Wang and Dispenzieri*.[1,2,11–14]

Conclusions

POEMS syndrome is a paraneoplastic syndrome associated with a clonal plasma cell neoplasm, and is generally considered a rare condition given its low prevalence. The diagnosis is especially challenging, but with an adequate clinical approach, supported by complementary studies focused on findings that identify the systemic involvement of the disease are enough, as well as the search for elements

that allow ruling out the main differential diagnoses, such as chronic inflammatory demyelinating polyneuropathy or light chain amyloidosis. To the extent that the diagnosis is made early, patients benefit more from treatment, since it decreases the progression of the disease and has an impact on survival.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical considerations

The authors declare that they have followed their center's protocols on the publication of patient data and have obtained the corresponding permissions. These cases reflect the clinical observations reported from 16 retrospective cases using the identified data, the patients in this case series were not involved in any study. This study is classified within the "no risk" category. No patient consent was required.

Patient consent (informed consent)

This study is classified within the "no risk" category. No patient consent was required.

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