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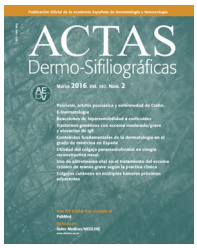

E-CASE REPORT

Glomeruloid Hemangioma and POEMS Syndrome☆

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KEYWORDS
Polyneuropathy;
Organomegaly;
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Skin abnormalities syndrome;
Glomeruloid hemangioma;
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Abstract POEMS syndrome is a paraneoplastic manifestation associated with hematopoietic disorders such as multiple myeloma and Castleman disease. POEMS is an acronym for the main clinical features of the syndrome, namely, Polyneuropathy, Organomegaly, Endocrinopathy, M protein, and Skin abnormalities. Glomeruloid hemangiomas are considered to be a specific clinical marker of POEMS syndrome. However, while they are not pathognomonic, their presence should raise suspicion of this syndrome or alert clinicians to its possible future development, as these lesions can appear years before the onset of the syndrome. We report the cases of 2 women with plasma cell dyscrasias and sudden onset of lesions with a vascular appearance and histologic findings consistent with glomeruloid hemangioma. Recognition of this vascular tumor is important for the early diagnosis of POEMS syndrome.

PALABRAS CLAVE
Síndrome de Polineuropatía;
Organomegalia;
Endocrinopatía;
M proteína;
Skin abnormalities;
Hemangioma glomeruloide;
Síndrome paraneoplásico

Hemangiomas glomeruloides y síndrome POEMS

Resumen El síndrome POEMS es una manifestación paraneoplásica asociada a procesos hematológicos como el mieloma múltiple y la enfermedad de Castleman. El acrónimo engloba las manifestaciones clínicas más frecuentes (*Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin abnormalities*). Dentro de las manifestaciones cutáneas, destaca por su especificidad la aparición de hemangiomas glomeruloides. Pese a no ser patognomónicos de la enfermedad, su aparición debe hacer sospechar la presencia del síndrome POEMS o su eventual desarrollo, ya que pueden aparecer años antes del desarrollo completo del síndrome. Presentamos 2 mujeres adultas con discrasias de células plasmáticas y aparición brusca de lesiones de aspecto vascular compatibles histológicamente con hemangiomas glomeruloides. Debemos reconocer la posible aparición de este tipo de tumores vasculares en los pacientes con síndrome POEMS para su diagnóstico precoz.

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Introduction

POEMS syndrome is a rare paraneoplastic phenomenon associated with various plasma cell dyscrasias. In addition to neurologic, hematologic, and endocrine manifestations, it presents a wide variety of cutaneous manifestations. Of the various forms of cutaneous involvement in POEMS syndrome, glomeruloid hemangiomas are notable for their specificity.

Case 1

The patient was a 50-year-old woman with a medical history of arterial hypertension, dyslipidemia, and polycythemia vera, for which she had undergone therapeutic phlebotomy on numerous occasions. She had also recently been diagnosed with hypothyroidism, for which she was receiving hormone replacement therapy. The patient was admitted to the hospital with a complaint of loss of strength in the lower limbs and associated paresthesia that had first appeared 6 months earlier and had progressively worsened. A diagnosis of mixed polyradiculoneuropathy had been established. A weak monoclonal IgA component and a lytic lesion on the left ilium were also found. After a bone marrow study and a positron emission tomography–computed tomography study, a diagnosis of solitary plasmacytoma was established. The patient also reported that numerous asymptomatic papular lesions had appeared on her trunk and upper limbs in the previous 2 months. Physical examination revealed multiple violaceous papules with a vascular appearance, a smooth surface, and an average diameter of 5 mm on the upper chest and on the medial aspect of the arms (Figure 1). Dermoscopic examination revealed milky-red areas and small reddish circular structures, some arranged in a linear pattern. Hypertrichosis on the jawline, the upper lip, and the dorsum of the hands and forearms was also present, as well as mild, diffuse hyperpigmentation in sun-exposed areas. Histopathologic examination of a papule revealed a dermal lesion composed of multiple formations with a glomeruloid appearance and 2 types of vessels. CD34-negative sinusoidal vessels were present in the central area and CD34-positive vessels with a capillary appearance, consistent with glomeruloid hemangioma, were present in the periphery. Vessels of both types were positive for CD31, CD68, and vascular endothelial growth factor (VEGF) (Figure 2). On the basis of these histologic findings, the presence of a solitary plasmacytoma together with a monoclonal IgA spike and mixed polyradiculoneuropathy, a diagnosis of POEMS syndrome was established.

Case 2

The patient was an 82-year-old woman with a history of arterial hypertension and IgM kappa multiple myeloma who was admitted to our hospital for treatment of pathologic fractures of the ribs and clavicle. The patient had a past history of pathologic fractures caused by multiple lytic bone lesions. A blood smear taken while the patient was in the hospital revealed that the percentage of plasma cells was 30%. Kidney failure associated with hypercalcemia was also detected. The patient was evaluated after numerous macules and papules with a vascular appearance and an intense erythematous-violaceous color appeared suddenly, over the course of 48 hours, on the submammary areas, abdomen, groin, and back (Figure 3). Dermoscopic examination revealed milky-red areas and small reddish circular structures. Additional testing ruled out coagulation disorders and the platelet count yielded no findings that explained the lesions. Histopathologic examination of a lesion revealed a proliferation of capillaries (some dilated); inside the lumen of some vessels were other small vascular lumens arranged in a glomerular pattern consistent with glomeruloid hemangioma (Figure 3). The endothelium of these vascular lumens was positive for CD31 and CD34. Despite treatment with thalidomide, systemic corticosteroids, and cyclophosphamide, the hematologic disease progressed and eventually caused the death of the patient.

Table 1 Skin Lesions Associated With POEMS Syndrome.

- Diffuse hyperpigmentation
- Raynaud syndrome
- Vascular tumors
  - Glomeruloid hemangiomas
  - Capillary angioma
  - Pyogenic granuloma
- Hypertrichosis
- Sclerodermiform changes

Discussion

POEMS syndrome is a paraneoplastic syndrome that occurs in monoclonal plasma cell dyscrasias and in Castleman disease.[1,2] *POEMS* is an acronym for the main clinical features of the disease: polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal gammopathy (M), and skin changes (S).

It usually affects middle-aged adults, predominantly men in some series.

There have been attempts to establish a series of diagnostic criteria for POEMS syndrome. These criteria have undergone modifications in recent years. It is generally accepted that 2 major criteria and at least 1 minor criterion must be met. The major criteria are polyneuropathy, monoclonal gammopathy, lytic bone lesions, an increase in VEGF, and the presence of Castleman disease. The minor criteria are organomegaly, endocrinopathy, skin changes, papilledema, and thrombocytosis.[3] However, a retrospective study showed that cases with an atypical presentation cannot be diagnosed using these criteria alone.[4]

Some of the most common cutaneous manifestations are as follows: diffuse cutaneous hyperpigmentation, hypertrichosis, sclerodermiform changes, acrocyanosis, hyperhidrosis, and vascular lesions (Table 1). Vascular lesions are present in up to a third of patients. Histologically, various types can be found: lobular capillary hemangioma, capillary angioma, multinucleate cell angiohistiocytoma, tufted angioma, and glomeruloid hemangioma.[5,6] A single excised surgical specimen can simultaneously have foci of several of these vascular tumor types. Therefore, there is thought to be a spectrum of hemangiomatous lesions associated with POEMS that present various degrees of endothelial proliferation in response to angiogenic stimuli.[7]

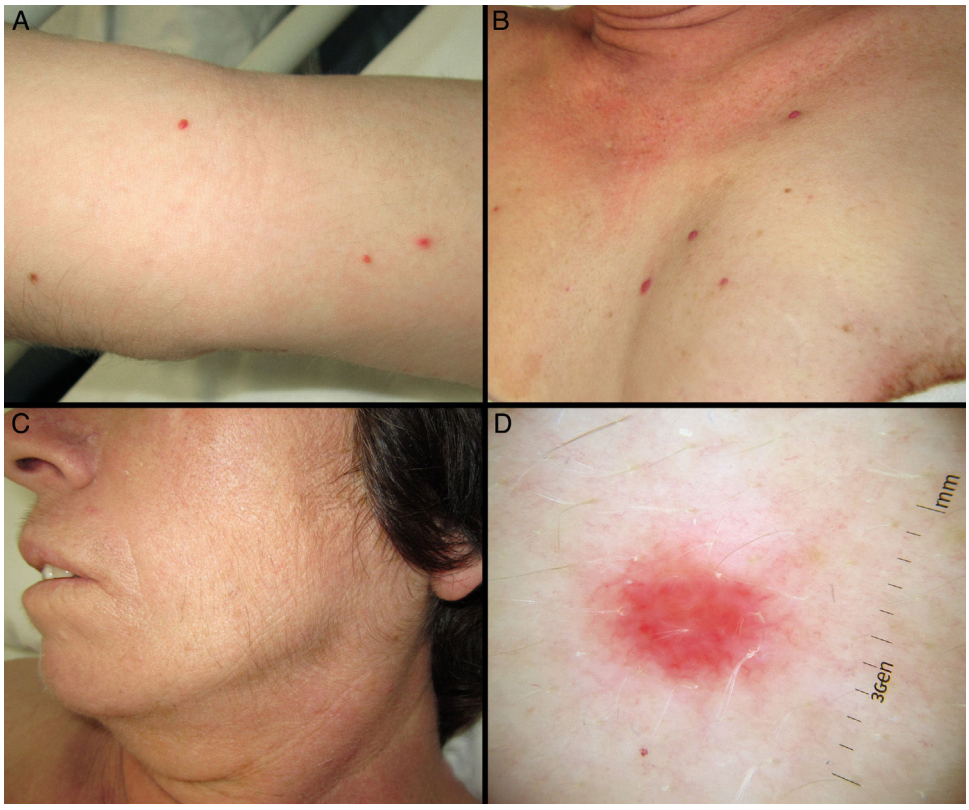

Figure 1 A and B, Violaceous, dome-shaped papules with a vascular appearance on the upper chest and arms. C, Hypertrichosis in the malar region. D, Dermoscopic image showing milky-red areas.

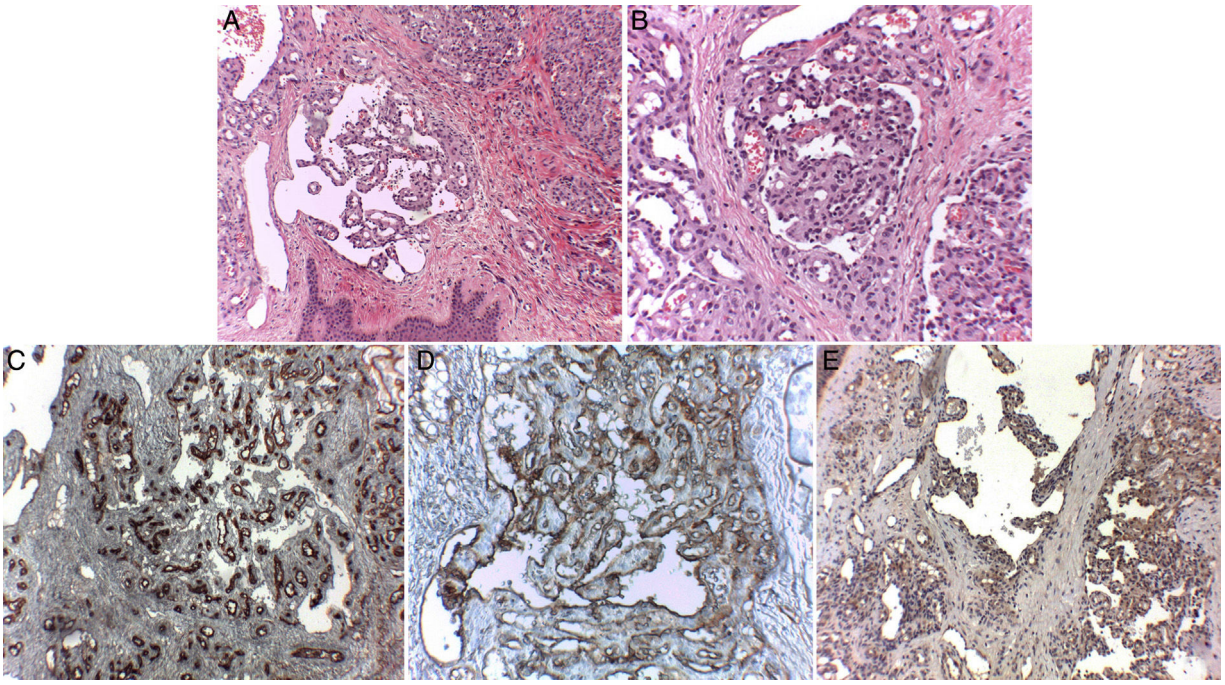

Figure 2 Pathologic examination of a papule from the upper chest. A, Multiple formations with a glomeruloid appearance in the dermis, hematoxylin-eosin, original magnification × 10. B, Image with greater detail, hematoxylin-eosin, original magnification × 20. C, Stain showing CD34-positive cells exclusively in the capillary vessels, hematoxylin-eosin, original magnification × 20. D, Stain showing CD31-positive cells in sinusoidal vessels and capillary vessels of the glomeruloid hemangioma, hematoxylin-eosin, original magnification × 20. E, Stain showing cells positive for vascular endothelial growth factor in both types of vessels, hematoxylin-eosin, original magnification × 20. gr2.

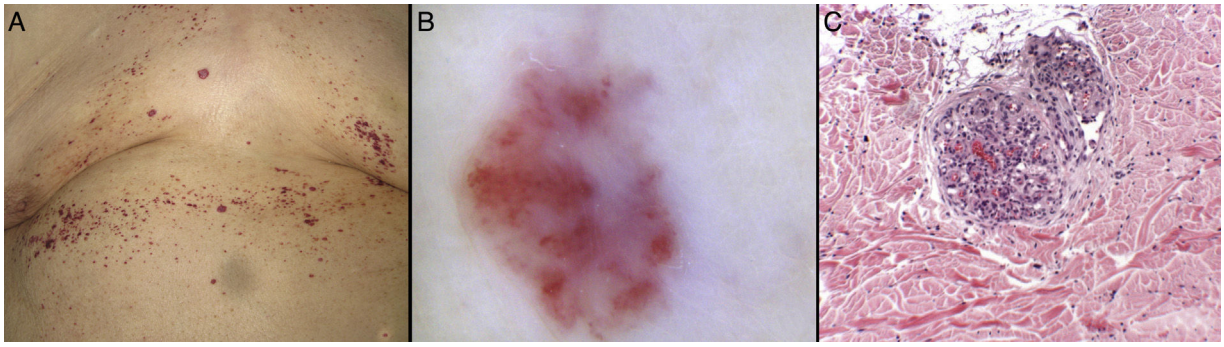

Figure 3 A, Multiple erythematous-violaceous macules and papules with a vascular appearance in the submammary and abdominal area. B, Dermoscopic image showing milky-red areas and reddish dots arranged in a linear pattern. C, Structures with a glomeruloid appearance in the dermis with the presence of peripheral sinusoidal vessels and capillaries that project towards the lumen of the vessel, hematoxylin-eosin, original magnification × 10. gr3.

Glomeruloid hemangioma, although rare, is the most specific cutaneous manifestation of POEMS syndrome and is strongly associated with the disease. These lesions tend to appear suddenly in the form of multiple violaceous, dome-shaped papules with a vascular appearance on the trunk and the proximal parts of the limbs. The sudden appearance of the lesions over the course of days or a few weeks helps doctors to associate glomeruloid hemangioma with POEMS syndrome because lesions that appear more gradually can be found in patients with no other associated symptoms. The lesions can also present as bluish subcutaneous nodules or cerebriform papules.[8]

Histopathologic examination reveals scattered, well-defined dermal structures of various sizes that resemble renal glomeruli, with a larger, dilated central vessel with a sinusoidal appearance surrounded by a series of small capillary vessels on the periphery.

The larger central vessels are formed by sinusoidal endothelial cells that are CD31-positive, CD68-positive, and CD34-negative.[9] The projections towards the interior of the vascular space are formed by capillary endothelial cells interspersed with stromal cells. Because of immunoglobulin deposition, these stromal cells present PAS-positive eosinophilic globules. Unlike the sinusoidal cells, the capillary endothelial cells are positive for CD31, CD68, and CD34.

As in our patient in Case 1, it has been shown that both kinds of endothelial cells express VEGF and its receptor, Flt-1,[10] supporting the theory that VEGF is a likely etiologic agent of the disease.

Several authors have described glomeruloid hemangiomas without associated POEMS syndrome,[11,12] but in many cases the follow-up period was relatively short. There have been reports of patients with glomeruloid hemangiomas that appeared up to 10 years before the onset of POEMS syndrome.[9,13]

The etiology and pathogenesis of POEMS syndrome do not depend on aberrant immunoglobulin production; instead, several factors are thought to be involved. Elevated production of proinflammatory cytokines (tumor necrosis factor-α, IL-6, IL-1β) would explain symptoms such as polyneuropathy, hyperpigmentation, and endocrine alterations. In patients with POEMS syndrome, there are higher concentrations of VEGF and metalloproteinases than in controls or in patients with multiple myeloma in isolation.[10,14] These 2 factors act in the endothelium and the smooth muscle cells, playing an important role in angiogenesis and neovascularization. VEGF is a selective mitogen for endothelial cells that is generally produced by platelets and plasma cells. It produces its mechanism of action through 2 VEGF receptors: VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1).

Glomeruloid hemangiomas are also sometimes associated with Castleman disease, a rare lymphoproliferative disorder. This disease has a proinflammatory cytokine profile similar to that of POEMS syndrome, justifying this association and the presence of similar symptoms.

For the treatment of POEMS syndrome, there are various beneficial therapeutic modalities: systemic corticosteroids, radiation therapy, and alkylating agents. Other more recent approaches are autologous hematopoietic cell transplantation, VEGF inhibitor, bevacizumab, and lenalidomide.

In conclusion, a diagnosis of glomeruloid hemangioma should always raise suspicion of POEMS syndrome. Patients with these lesions should be followed up over a long period of time in order to rule out associated hematologic diseases.

Ethical Disclosures

Protection of persons and animals. The authors declare that no experiments were performed on humans or animals for the purpose of this study.

Data confidentiality. The authors declare that they followed their hospital's regulations regarding the publication of patient information.

Right to privacy and informed consent. The authors declare that no private patient data appear in this article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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