

Glomeruloid hemangioma in POEMS syndrome: a report on two cases and a review of the literature *

Hemangioma glomeruloide e a síndrome POEMS. Relato de dois casos e revisão da literatura

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Abstract: Glomeruloid hemangioma is characterized by coiled capillary vessels contained within enlarged vascular spaces displaying an architecture that resembles renal glomeruli. The condition is strongly associated with POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin changes). The present paper reports on two cases of glomeruloid hemangiomas associated with POEMS syndrome, and includes a review of the literature. Case one refers to a 63-year old female patient admitted to hospital with ascites, hepatosplenomegaly, walking difficulties and cutaneous hemangiomas. Histopathology revealed a diagnosis of glomeruloid hemangioma and served to guide the clinical work-up, which revealed sensorimotor polyneuropathy, a plasmacytoma in the L4 vertebra with tumor cells positive for kappa chain, and diabetes mellitus. These findings permitted a diagnosis of POEMS syndrome to be reached. The second case consisted of a 39-year old woman admitted to hospital with edema, ascites, pleural effusion, glomeruloid hemangiomas and lymphadenopathy (Castleman's disease). Additional findings included monoclonal IgG-lambda paraproteinemia, blastic lesions in the right iliac bone and L4 vertebra, and demyelinating sensorimotor neuropathy affecting all four limbs. The final diagnosis in this case was POEMS syndrome associated with Castleman's disease.

Keywords: Dermatology; Giant lymph node hyperplasia; Hemangioma; POEMS syndrome; Pathology

Resumo: O hemangioma glomeruloide caracteriza-se por enovelados capilares contidos em espaços vasculares dilatados remissivos de glomérulos renais, sendo fortemente associado à síndrome POEMS (polineuropatia, organomegalia, endocrinopatia, gamopatia monoclonal e alterações cutâneas). Relatam-se dois casos da síndrome associados a hemangiomas glomeruloides e faz-se uma revisão da literatura. O primeiro é uma paciente feminina, 63 anos, internada para investigação de ascite, hepatoesplenomegalia, dificuldade de deambulação e hemangiomas cutâneos. A histopatologia de uma dessas lesões estabeleceu o diagnóstico de hemangioma glomeruloide e direcionou a investigação, que revelou polineuropatia sensitivo-motora, plasmocitoma kappa-positivo em L4 e *Diabetes mellitus*, permitindo o diagnóstico da síndrome. O segundo caso é de uma paciente feminina, 39 anos, com edema, ascite, derrame pleural, hemangiomas glomeruloides e linfonodomegalias (doença de Castleman). Havia um componente monoclonal de IgG-lambda e lesões blásticas no íliaco direito e em L4, assim como lesão desmielinizante sensitivo-motora nos quatro membros, compondo o diagnóstico de síndrome POEMS.

Palavras-chave: Dermatologia; Hemangioma; Hiperplasia do linfonodo gigante; Patologia; Síndrome POEMS

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INTRODUCTION

POEMS syndrome is the paraneoplastic clinical manifestation of a monoclonal plasma cell dyscrasia, its acronym being derived from some of its principal characteristics: Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin changes. It affects both males and females of around 50 years of age, with the largest number of cases having been described in the Japanese population. Various skin alterations have been described, the most common being hyperpigmentation and hypertrichosis. Cutaneous hemangiomas are present in around one-third of cases and may consist of the strawberry nevus, lobular capillary hemangioma or glomeruloid hemangioma types. Although they are present in only 3% of cases, glomeruloid hemangiomas are strongly associated with POEMS syndrome and, when present, contribute to reaching an early diagnosis. The present paper reports on two cases of POEMS syndrome. In the first case, diagnosis was based on the histopathology finding of a glomeruloid hemangioma, whereas in the second case the presence of this proliferation contributed towards establishing diagnosis of the syndrome.

CASE REPORTS

Case 1

A 63-year old female patient was referred to the internal medicine department of the Federal Hospital of Bonsucesso (Ministry of Health) to investigate the presence of ascites, hepatosplenomegaly and difficulty in walking, symptoms that had been becoming progressively worse over the past two years. While in hospital, asymptomatic, erythematous, violaceous papules with an angiomatous appearance, measuring



FIGURE 2: Erythematous, violaceous papule with an angiomatous appearance, located in the left scapular region

around 1 cm in diameter, were found on her chest. The patient reported that they had been present for the past four years (hence preceding her principal complaint by two years). A dermatology report was requested (Figures 1 and 2). Diagnostic hypotheses consisted of strawberry nevus, bacillary angiomatosis or Kaposi's sarcoma, and biopsies were made of two of these lesions. Histopathology revealed a vascular proliferation in the superficial and deep dermis composed of coiled capillaries inside large vascular spaces lined with a single layer of endothelial cells in patterns that resemble those of renal glomeruli (Figures 3 and 4). A diagnosis of glomeruloid hemangioma was made followed by a recommendation to investigate for



FIGURE 1: Two erythematous, violaceous papules with an angiomatous appearance located on the right breast and in the presternal region

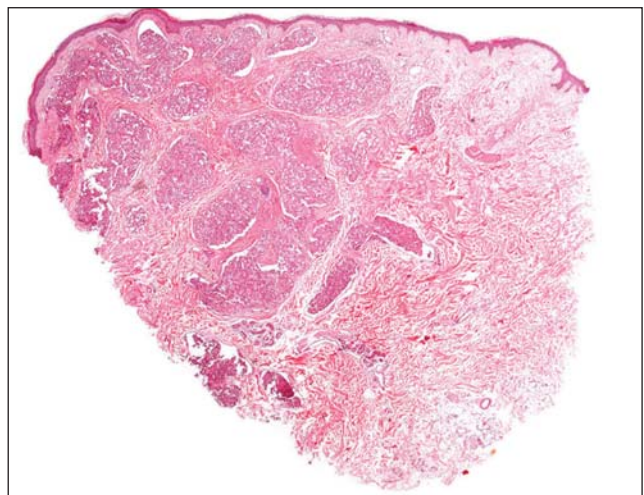


FIGURE 3: Vascular proliferation in the superficial and deep dermis composed of coiled capillaries inside large vascular spaces. HE, 20x, original magnification

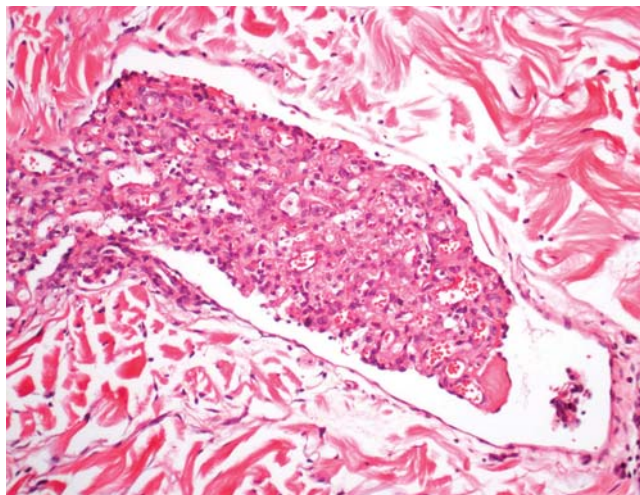


FIGURE 4: Coiled capillaries inside a large vascular space lined externally with a single layer of endothelial cells and resembling a renal glomerulus. HE, 200x, original magnification

POEMS syndrome. When the patient was reevaluated, findings consisted of: sensorimotor axonal polyneuropathy at electromyography; an osteosclerotic lesion in L4 resulting from a plasmacytoma with tumor cells positive for kappa chain; absence of a monoclonal spike on serum protein electrophoresis; diabetes mellitus; a prior history of papilliferous carcinoma of the thyroid gland treated by total thyroidectomy, and hepatosplenomegaly. These findings constituted a diagnosis of POEMS syndrome. The patient was referred to the National Cancer Institute (INCA) for treatment of the plasmacytic neoplasm.

Case 2

A 39-year old female patient was admitted to the Clementino Fraga Filho Teaching Hospital of the Federal University of Rio de Janeiro reporting progressive dyspnea that had begun a few days prior to her admission to hospital. Two years previously, she had developed swelling in her lower limbs which, at the present time, extended as far as her knees, associated with skin lesions, an increase in abdominal circumference and periorbital puffiness in the mornings.

A physical examination revealed six erythematous, violaceous, angiomatic papules, each measuring 0.5 cm in diameter, on the back of her neck, trunk, abdomen and on her right forearm. Palpable lymph nodes of 0.5 – 2.0 cm were found in the left axillary region, anterior cervical chains and in the right submandibular region. All were pliable, moveable and painless. Ascites and hepatosplenomegaly were present. Neurological examination revealed generalized deep hyporeflexia, with tonus and muscle strength preserved; superficial distal hypoesthesia in the feet and distal paresthesia in all four limbs.

Serum protein electrophoresis showed a monoclonal IgG-lambda paraprotein, while serum immunoglobulin levels were within normal limits. Electromyography confirmed a diffuse, symmetrical demyelinating lesion of the sensorimotor fibers affecting all four limbs, with an associated axonal lesion in the lower limbs. X-ray images revealed two blastic lesions, one on the right iliac close to the roof of the acetabulum and the other in the L4 vertebral body (Figure 5). Tomography of the chest and abdomen showed paratracheal, precarinal and subcarinal lymphadenopathy, a small bilateral pleural effusion, pericardial effusion, mild ascites, splenomegaly and small retroperitoneal lymph nodes.

Biopsy of a lymph node from the left axillary chain showed a follicular proliferation pattern, with thickening of the mantle zone and formation of concentric rings of lymphocytes surrounding the germinal centers, which were hyalinized, atrophic and centralized by a blood vessel (resembling a lollipop). Vascular proliferation was found, together with sinus histiocytosis in the interfollicular parenchyma and an absence of plasma cells. Diagnosis was compatible with the hyaline vascular variant of Castleman's disease (angiofollicular lymph node hyperplasia). Bone marrow aspiration failed to show any infiltration.

A biopsy of the skin lesion was also performed, revealing a proliferation of coiled capillary vessels in the dermis, contained within large, dilated vascular spaces, with numerous eosinophilic globules, thus characterizing a glomeruloid hemangioma (Figures 6 and 7). Taken together, these findings led to a diagnosis of POEMS syndrome, in this case associated with Castleman's disease. The patient was referred to the hematology unit for treatment.



FIGURE 5: Anteroposterior x-ray image of the hipbone showing a blastic lesion on the right iliac close to the roof of the acetabulum

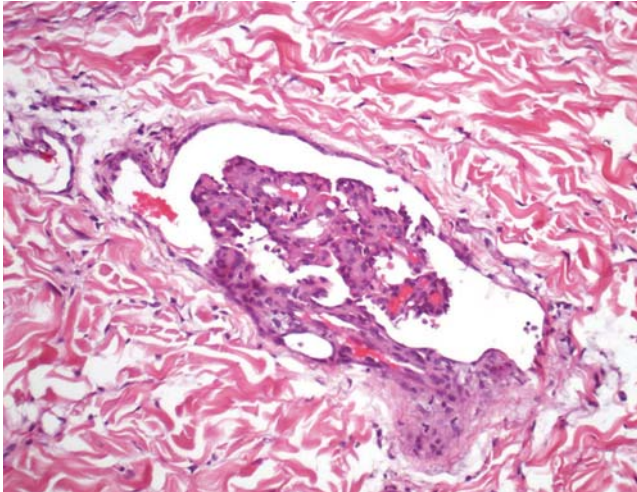


FIGURE 6: A group of capillary vessels contained within a dilated vascular space, resembling a renal glomerulus. HE, 200x, original magnification

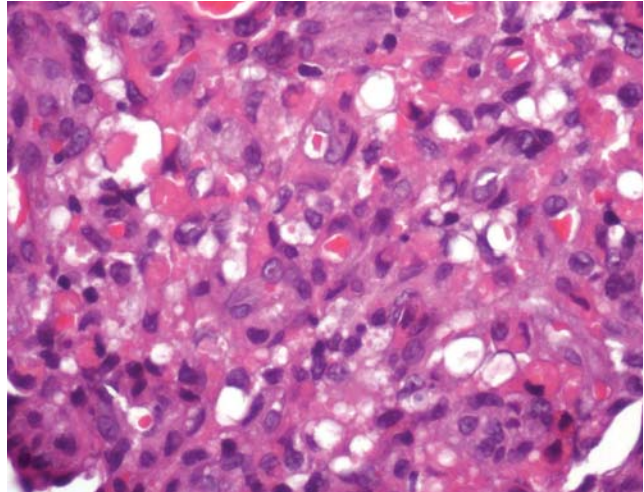


FIGURE 7: Detail of the vascular proliferation showing eosinophilic globules amidst endothelial cells. HE, 400x, original magnification

DISCUSSION

Hemangiomas in POEMS syndrome

Great emphasis is currently given to the association of POEMS syndrome with the presence of multiple skin angiomas. These are located on the trunk and on the proximal segments of the limbs. They are erythematous, violaceous or brownish in color and may range in size from millimeters to a few centimeters.¹ They are believed to be present in an estimated 24-48% of individuals with POEMS syndrome and may be of the strawberry nevus, lobular capillary hemangioma or, less commonly, of the glomeruloid hemangioma (GH) types. GH is a benign vascular neoplasia with a very characteristic appearance at histopathology in which coiled capillaries occupy a large dilated vascular space in the dermis, lined externally by a single layer of endothelial cells, resembling a renal glomerulus. PAS-positive eosinophilic globules may be found amidst the endothelial cells and light chain deposits have already been identified in the coiled capillaries in the immunohistochemical evaluation of some cases. Although present in only 3% of cases, GH is considered to represent an important cutaneous marker of POEMS syndrome. A review of the pertinent literature revealed 25 previously published cases, 16 of which were associated with the syndrome, while in 5 cases Castleman's disease was also present.²⁻⁹ In one case, a diagnosis of Castleman's disease was made but the minimum criteria for a diagnosis of POEMS syndrome were not present; however, the patient continued to be monitored.⁴ GH may sometimes precede the other signs and symptoms of this syndrome, permitting an early diagnosis to be reached or constituting a link between a constellation of clinical findings that, in principle, may appear to be unrelated to each other. In cases in which GH alone

was found, it has been questioned whether a diagnosis of POEMS syndrome could perhaps become evident after years of follow-up.⁶

Clinical manifestations of POEMS syndrome

The first reference of POEMS syndrome in the literature dates from 1938, when a case was reported of a patient with symptoms of sensorimotor neuropathy, hyperpigmentation, increased cerebrospinal fluid (CSF) protein levels and a single plasmacytoma. In 1956, Crow described two patients with osteosclerotic plasmacytoma, peripheral neuropathy, increased CSF protein levels and hyperpigmentation, characterizing a clinical condition that was later referred to as Crow-Fukase syndrome. It was in 1980 that Bardwick first coined the acronym POEMS, giving emphasis to the principal components of this syndrome. Since no laboratory markers exist, diagnosis is based on the presence of major and minor criteria, as shown in Table 1.

All the patients with POEMS syndrome have peripheral neuropathy, this being an obligatory criterion for diagnosis of the disease. Neuropathy is characterized by being of the thick-fiber, sensorimotor type with a demyelinating pattern that initially manifests itself as a distal symmetric sensory alteration, with paresthesia and sensations of pins and needles and cold, followed by a distal and symmetrical loss of muscle strength.¹ Electromyography shows a pattern that is characteristic both of a demyelinating disease and of axonal degeneration.

Organomegaly is present in at least 50% of patients and may present as an enlarged liver, spleen or lymph nodes (reactive pattern or in association

with Castleman's disease).^{1,10,11}

In a study conducted by Dispenzieri, 66/99 patients (67%) had some form of endocrine abnormality.¹ Similar findings have also been reported by other investigators, the most frequent manifestations being diabetes mellitus and hypothyroidism.^{10,11} Other endocrine abnormalities reported consist of alterations in the gonadal axis, alterations in the adrenal axis, hyperprolactinemia, gynecomastia or galactorrhea and hyperparathyroidism.

The presence of monoclonal gammopathy constitutes another obligatory criterion for the diagnosis of POEMS syndrome. Patients usually present with high serum M-protein concentrations (a monoclonal spike), as found in 75% and 85% of individuals in the studies conducted by Nakanishi and Dispenzieri, respectively.^{1,11} The presence of gammopathy has also been shown using urine protein electrophoresis, immunofixation and immunohistochemistry performed on material obtained at biopsies of osteosclerotic lesions. In the study conducted by Dispenzieri, all 97 individuals analyzed had lambda (λ) light chains, 44 of which were of the IgA type, 40 of the IgG type and 1 of the IgM type.¹ In 12 patients, the presence of a light chain was not detected in serum or urine, with diagnosis of the disease being made on the basis of the biopsy results from the bone lesion. Although less common, plasma cell dyscrasia may also be of kappa-type light chains, as occurred in case #1.¹² Bone lesions are present in the majority of individuals with POEMS syndrome and may be single or multiple. They are normally painless (unlike the bone lesion found in cases of multiple myeloma). They are generally of the sclerotic type; however, they may be mixed (lytic lesions with a sclerotic margin) and, in rare cases, purely lytic. The sites most commonly affected are the spine, the pelvic bones and the ribs, whereas the bones of the cranium and limbs remain unaffected. Bone marrow biopsy findings are generally nonspecific, suggestive of reactive bone marrow hyperplasia.¹

The skin alterations in POEMS syndrome have been well defined in the literature, with various other known alterations in addition to the angiomas. The most common are diffuse cutaneous hyperpigmentation, acrocyanosis and plethora. Other manifestations include thickening of the skin (of the sclerodermiform type), hypertrichosis, necrotizing vasculitis, hyperhidrosis and leukonychia, in addition to calciphylaxis and cicatricial alopecia. The hyperpigmentation is due to an increase in melanin production with the habitual number of melanocytes and is similar to that found in Addison's disease.¹³ It may be diffuse (more common) or localized, developing principally on the extensor surfaces, back, neck and axillae. It usually

regresses in response to treatment of the disease. Hyperhidrosis is generally localized, whereas hypertrichosis is diffuse and may constitute a primary manifestation of the disease or occur secondary to an endocrine abnormality. The association between POEMS syndrome and skin thickening of the sclerodermiform type on the hands and feet has also been reported in association with other symptoms such as Raynaud's phenomenon and sicca syndrome.¹⁴ Leukonychia is a very rare manifestation that occurs simultaneously with finger clubbing in pulmonary hypertension. The cicatricial alopecia was of the secondary type, since it developed in an area adjacent to an osteosclerotic lesion on the cranium. In 1995, the association of calciphylaxis with osteosclerotic myeloma was first described and in 2004 De Roma reported the first case of a patient with POEMS syndrome (diagnosed two and a half years previously) who developed calciphylaxis in the absence of end-stage renal disease or hyperparathyroidism.¹⁵

Physiopathology

POEMS syndrome is intimately related to an underlying plasma cell dyscrasia, although the anomalous production of immunoglobulin does not contribute to the genesis of the clinical findings. Experimental studies have found that the chronic and sustained elevation of proinflammatory cytokines such as TNF- α , IL-1 β , IL-6 and an imbalance of inflammatory and anti-inflammatory cytokines are responsible for many of the manifestations of this disease. TNF- α is associated with demyelinating peripheral neuropathy, hepatosplenomegaly, endocrine dysfunction, edema, weight loss, hypertriglyceridemia and diarrhea. Elevated IL-1 β levels cause cachexia, anorexia, skin pigmentation through activation of the proopiomelanocortin gene, glucose intolerance, behavioral and psychiatric disorders and acceleration of atherosclerosis. IL-6 is related to plasma cell proliferation and monoclonal gammopathy, thrombocytosis, Castleman's disease, hemangiomas and microangiopathic glomerulopathy.¹⁶ Serum IL-6 levels in 6 patients with active POEMS syndrome were shown to be higher than those of patients in whom the disease was stable. Furthermore, IL-6 levels increased prior to each exacerbation in clinical symptoms.¹⁷

Other mediators involved in the pathogenesis of this syndrome include vascular endothelial growth factor (VEGF), the metalloproteinases (MMPs) and the tissue inhibitor of MMPs (TIMP-1).^{18,19} It has already been shown that VEGF concentrations are higher in POEMS syndrome compared to normal controls or to patients with multiple myeloma, Waldenström macroglobulinemia or other neurological diseases, and they appear to contribute to the development of

TABLE 1: Diagnostic criteria for POEMS syndrome

Major	Polyneuropathy Monoclonal plasma proliferative disorder
Minor	Sclerotic bone lesions Castleman's Disease Organomegaly (Hepatomegaly, splenomegaly, lymphadenopathy) Edema / serous effusion Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) Skin changes (hyperpigmentation, hypertrichosis, plethora, cutaneous hemangiomas, sclerodermiform changes) Papilledema
Other known associations	Finger clubbing, weight loss, thrombocytosis, polycythemia, hyperhidrosis,
Possible associations	Primary pulmonary arterial hypertension, obstructive pulmonary disease, thrombosis, arthralgias, cardiomyopathy, fever, diarrhea, hypovitaminosis B12

Diagnosis requires the mandatory presence of the two major criteria plus at least one minor criterion

angiomas in the syndrome.^{3,18}

Metalloproteinases and VEGF play a crucial role in angiogenesis and neovascularization, acting on the endothelial cells and on the cells of the vascular smooth muscle. The platelets and plasma cells are the principal sources of VEGF, a potent inducer of vascular permeability. One study showed a reduction in serum VEGF levels in 7/10 patients with POEMS syndrome following conventional therapy.²⁰ The role of VEGF in inducing MMP production by the endothelial cells and the vascular smooth muscle cells is already known. TIMP acts by regulating the effect of the MMPs on the extracellular matrix of the endothelial cells, thus explaining the vascular damage caused by them. The imbalance between the two appears to lead to the development of certain neurological diseases, including autoimmune neuropathies. Higher levels of these substances were found in patients with POEMS syndrome compared to healthy controls and to patients with other neurological diseases, with concentrations decreasing abruptly following treatment.¹⁹

POEMS syndrome is often associated with Castleman's disease, an atypical lymphoproliferative disorder of undetermined cause. Diagnosis is based exclusively on histopathology, which is characterized by angiofollicular lymph node hyperplasia, either with

or without multisystem alterations. The strong similarity between the profile of inflammatory cytokines present in POEMS syndrome and that found in Castleman's disease justifies the frequency of their association, as well as the overlapping of symptoms.

CONCLUSION

POEMS syndrome involves a large number of dermatological manifestations of which glomeruloid hemangioma is the most specific. The dermatologist may be the first specialist consulted by these patients or the patients may be referred from other specialist clinics. Although the various clinical findings may at a certain moment appear to be unrelated, it is of crucial importance to integrate all of these findings in order to recognize the syndrome. The histopathological diagnosis of glomeruloid hemangioma may represent the piece that was missing from the jigsaw puzzle. We therefore suggest that every histopathology report of glomeruloid hemangioma be issued with an accompanying note recommending investigation for POEMS syndrome and Castleman's disease. Even if the investigation proves negative, reevaluation of these patients over time is imperative, since glomeruloid hemangiomas may precede the other findings of this syndrome by several years. □

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