

POEMS and calciphylaxis: a novel association?

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The term monoclonal gammopathy refers to a heterogeneous group of hematologic malignancies that include monoclonal gammopathy of undetermined significance (MGUS), plasmacytoma, multiple myeloma, and lymphoma. Other rare diseases, namely primary amyloidosis and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin abnormalities) syndrome, also belong to the group of monoclonal gammopathies. Knowledge on pathogenesis, prognosis and treatment of MGUS, multiple myeloma and primary amyloidosis has been progressively expanding during the last decade. Conversely, as of to date, POEMS syndrome is still a poorly understood disease in terms of biology and clinical course.

POEMS is a paraneoplastic syndrome resulting from an underlying plasmaproliferative disorder¹. The characteristic neoplastic lesion is an osteosclerotic plasmacytoma which occurs either as a single or a multiple lesion in the bone marrow. Similar to the case of solitary plasmacytoma of the bone, in POEMS the bone marrow not involved by the osteosclerotic lesion usually contains < 5% polyclonal plasma cells¹. Plasmacytoma cells produce a monoclonal immunoglobulin A or G in 90% of cases, while the remaining cases secrete only light chains. Curiously, all cases of POEMS display a lambda light chain restriction, although molecular data on the preferential usage of specific lambda genes are still missing²⁻⁴.

The paraneoplastic manifestations associated with osteosclerotic plasmacytoma have been reported by several authors since 1938. These include peripheral neuropathy that is observed in all cases, accompanied by a constellation of signs and symptoms such as organomegaly (hepato-splenomegaly and lymphadenopathy), edema or effusions in body cavities, endocrinopathy, hypertrichosis, hyperpigmentations, sclerosis and other skin abnormalities, papilledema and clubbing⁵. In 1980, Bardwick et al. coined the acronym POEMS to represent a syndrome

characterized by polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal gammopathy (M) and skin abnormalities (S)⁵.

POEMS syndrome is a rare disease, since its prevalence, although still not well defined, has been estimated to be < 1% in cases of monoclonal gammopathies^{1,3}. However, the true prevalence of POEMS syndrome may be underestimated, since no single test establishes the diagnosis, but a high clinical suspicion is necessary to link the disparate signs and symptoms that characterize the disease. Recently, researchers at the Mayo Clinic revised the clinical criteria for the diagnosis of POEMS syndrome on the bases of a large mono-institutional series, and suggested that polyneuropathy and plasma cell disorder, associated with at least one additional minor criteria (Table I), are necessary for the diagnosis². The heterogeneity and complexity of the presenting features of POEMS syndrome are also documented by the existence of several clinical conditions which, although without diagnostic relevance based on the above-mentioned criteria, have been found to be associated to POEMS syndrome².

Activation of the proinflammatory cytokine network has been implicated in the pathogenesis of POEMS syndrome. Indeed, serum levels of interleukin (IL)-1 β , IL-6 and tumor necrosis factor (TNF)- α are increased in patients affected by POEMS syndrome and a correlation has been found between cytokine levels and disease activity^{6,7}. Proinflammatory cytokines may be the causative agents of the characteristic hallmarks of the syndrome, including endocrine abnormalities, skin changes, constitutional symptoms, edema, effusions, clubbing and organomegaly^{6,7}. The site of proinflammatory cytokine production is unknown, nevertheless some lines of evidence suggest that the microenvironment, rather than the plasma cell clone, is responsible for the production^{6,7}. This scenario appears to closely mimic multiple myeloma, in which cytokine production is mainly ascribed to stromal and accessory cells in the microenvironment rather than to the plasma cell population itself.

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TABLE I. Criteria for the diagnosis of POEMS syndrome².

<i>Major criteria</i>
Polyneuropathy
Monoclonal plasmaproliferative disorder
<i>Minor criteria</i>
Sclerotic bone lesions
Castleman disease
Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
Edema (edema, pleural effusion, or ascites)
Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)
Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomas, white nails)
Papilledema
<i>Known associations</i>
Clubbing
Weight loss
Thrombocytosis
Polycythemia
Hyperhidrosis
<i>Possible associations</i>
Pulmonary hypertension
Restrictive lung disease
Thrombotic diatheses
Arthralgias
Cardiomyopathy (systolic dysfunction)
Fever
Low vitamin B ₁₂ values
Diarrhea

In addition to IL-1 β , IL-6 and TNF- α , some data suggest that vascular endothelial growth factor (VEGF) is a candidate pathogenetic factor in POEMS syndrome^{8,9}: *i*) VEGF serum levels are increased in POEMS syndrome, but not in other monoclonal gammopathies; *ii*) serum levels are restored to normality after resection or radiation of the osteosclerotic plasmacytoma, suggesting that VEGF is presumably secreted by clonal plasma cells; *iii*) VEGF may account for edema and effusions by altering endothelial permeability, and may also induce organomegaly by increasing parenchymal vascular proliferation and skin alterations producing angiomas^{8,9}.

Ten to 30% of cases of POEMS syndrome are associated with generalized lymphadenopathy displaying the clinico-pathologic features of multicentric Castleman disease, a lymphoproliferation driven by human herpes virus 8 (HHV8)^{1,2}. The identification of HHV8 infection in tissue biopsy of POEMS syndrome associated with multicentric Castleman disease suggests a potential pathogenetic role of HHV8 via the production of IL-6 encoded by the viral IL-6 gene¹⁰.

In this issue of *Annali*, De Roma et al.¹¹ describe for the first time the association between POEMS syndrome and calciphylaxis. Calciphylaxis is a syndrome characterized by ischemic ulceration of the skin due to metastatic calcification of subcutaneous tissues and small arteries as a

consequence of hyperparathyroidism in end-stage renal disease¹². Calciphylaxis has been observed very rarely outside the context of uremia. The case reported by the authors developed calciphylaxis 34 months after the diagnosis of POEMS syndrome. The peculiarity of this case report is that calciphylaxis occurred in the absence of any of the known risk factors for calciphylaxis, such as end-stage renal disease, obesity, diabetes, elevated phosphorus level, treatment with warfarin, protein C and S deficiency or high parathyroid hormone levels¹¹. This suggests a possible pathogenetic link between calciphylaxis and POEMS syndrome, thus expanding the spectrum of conditions associated with this syndrome.

De Roma et al.¹¹ postulate that the association of calciphylaxis and POEMS syndrome might be a consequence of the impact of VEGF and/or proinflammatory cytokine deregulation in calcium homeostasis. The hypothesis of De Roma et al. is of certain interest, but at the same time is mainly speculative and raises some issues that prompt further investigations.

First, the pathophysiology of vascular calcification is complex, since it involves vascular smooth muscle cells and myofibroblasts and is due to a local imbalance between promoters and inhibitors of calcification in addition to systemic mechanic, endocrine, metabolic and inflammatory factors¹³. At present, the predominant view holds that end-stage renal disease-related calciphylaxis is triggered by elevated serum phosphorus levels which induce vascular smooth muscle cells to express genes, namely osteocalcin and osteopontin, that, in turn, promote calcium deposition¹². Conversely, solid evidence supporting the role of VEGF or cytokines on calciphylaxis is still lacking. Unluckily, De Roma et al.¹¹ failed to perform serological studies aimed at testing the levels of VEGF and of other cytokines in their patient. Also, the level of expression of genes involved in homeostasis of calcium deposition was not assessed on skin biopsy by appropriate immunohistochemical or molecular studies.

A second issue that remains unclear concerns the reason for prothrombin time prolongation in the case investigated by De Roma et al.¹¹. In this respect, it should be noted that some reports have documented an association between vitamin K deficiency and calciphylaxis. On these bases, it has been speculated that vitamin K deficiency disrupts a protein of the cellular matrix (MGP) that inhibits calcification and requires γ -carboxylation for its activity¹².

Finally, De Roma et al.¹¹ do not describe the patient treatment and outcome. The aim of the treatment in POEMS syndrome is to induce remission of both the plasma cell dyscrasia and the paraneoplastic syndrome. Several treatment options have been investigated, including radio-

therapy on osteosclerotic lesions, conventional alkylating agent-based chemotherapy and, in the last years, high dose melphalan and autologous stem cell transplantation^{2,14}. In the case reported by De Roma et al.¹¹, description of calciphylaxis response to a treatment tailored to plasma cell dyscrasia would have been useful to empirically corroborate the hypothesis of an association between POEMS syndrome and calciphylaxis.

In spite of these experimental limitations, the novel association between POEMS syndrome and calciphylaxis proposed by De Roma et al. is potentially interesting, since it points to the large spectrum of atypical presentations of this monoclonal gammopathy and prompts investigations aimed at defining the pathogenetic mechanisms involved in vascular calcification in this clinical context.

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