Polyneuropathy, Organomegaly, Endocrinopathy, M protein, Skin changes: not always a POEMS syndrome

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POEMS or Crow-Fukase syndrome is a rare plasma cell disease with multiorgan involvement, whose acronym refers to the presence of Polyneuropathy, Organomegaly, Endocrinopathy, M protein, Skin changes.[1] The etiology of POEMS is still unknown, but increasing evidence points to a possible role of Vascular Endothelial Growth Factor (VEGF). Serum VEGF levels have repeatedly been found to correlate with the clinical course and response to therapy.[2-4] Lacking specific tests or patognomonic signs, the diagnosis of POEMS syndrome is still based on the combination of clinical findings,[5] although general consensus has still to be reached.[6] Additional diagnostic markers other than clinical are therefore warranted. We herein report a patient who, although presenting all the POEMS features, was eventually diagnosed with a different disease. VEGF serum levels were in normal range and remained low despite the worsening of the disease. A 64-year-old man came to our attention after 4 month history of progressive scleroderma-like skin thickening, hyperpigmentation at the four limbs, chest and face, hypertrichosis, fever, distal painful paraesthesias at lower limbs. There was a recent onset of type II diabetes. Physical examination revealed hepatomegaly, unsteady gait, absent deep tendon reflexes, distal sensory loss. Electrodiagnostic study showed evidence of demyelinating polyneuropathy, with slowing or absence of conduction velocities and prolonged distal latencies. Immunoelectrophoresis evidenced an IgG lambda monoclonal gammopathy (2,6 g/L). Scleroderma-specific autoantibodies were negative. Mild and transient blood eosinophilia (800/μL) was present, which spontaneously resolved before any specific treatment. Bone marrow biopsy was normal, apart from a mild polyclonal plasmacytosis (plasma cells < 10%). Chest and abdominal CT scan confirmed hepatomegaly. Bone window CT images as well as whole-body PET scan were negative. The sclerodermic-like skin, although already reported in POEMS syndrome,[7] prompted us to perform a skin biopsy. The histology showed lymphoid infiltration of the small vessel in the derma. Serum VEGF (ELISA) was 828 pg/mL (Figure). The platelet number was within the normal range. A diagnosis of POEMS was proposed. The symptoms worsened, despite steroids and the patient could no longer work (as a carpenter) and manage his daily activities. VEGF dosage remained within the normal range (371 pg/mL - see the accompanying Figure). A diagnosis of eosinophilic fasciitis was eventually made. Started on methotrexate and cyclosporin-A, associated with low dose prednisone, skin induration and hyperpigmentation improved, as well as the painful paraesthesias. After 8 months, the patient was able to resume his job and his quality of life was back to normal. The patient presented all the POEMS clinical features, with the notable exception of the lack of clonal plasma cells proliferation in the bone marrow and the unusual vasculitic finding in the skin biopsy. VEGF serum levels were within the normal range, and persisted low despite the worsening of the disease. This behaviour was unusual for POEMS syndrome further supporting the possibility of a different diagnosis. Although a formal proof of the pathogenic role of VEGF in POEMS syndrome is still lacking, we previously described a correlation between high serum and peripheral nerve VEGF levels and clinical course as well as nerve damage in POEMS syndrome,[4] suggesting not only a putative pathogenic, but also a diagnostic and prognostic role of VEGF. In this regard, it is worth mentioning the recent report by Badros *et al.* describing a patient with POEMS syndrome whose symptoms recovered following therapy with Bevacizumab, a monoclonal antibody to VEGF.[8] We suggest that VEGF serum levels might be considered as an additional, supportive criterion for the diagnosis of POEMS syndrome, particularly when unusual clinical features are present.

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