

POEMS Syndrome with Calciphylaxis: A Case Report

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POEMS syndrome is a paraneoplastic syndrome caused by an underlying lymphoproliferative disorder. It is characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormalities. Cutaneous manifestations include hyperpigmentation, hypertrichosis, skin thickening, multiple glomeruloid angiomas, flushing, dependent rubor, acrocyanosis, white nails and clubbing (1). Calciphylaxis is a vasculopathy characterized by calcification of small-to-medium-sized blood vessels in the subcutis with intimal hyperplasia and thrombus formation. It occurs mainly in patients with chronic renal failure or hyperparathyroidism. The association of calciphylaxis with POEMS syndrome has been reported (2). We herein describe a case of calciphylaxis in a POEMS syndrome patient with no known predisposing factors for calciphylaxis, and discuss the link between the two conditions.

CASE REPORT

A 46-year-old man was diagnosed with POEMS syndrome in 2001 with initial presentation of progressive lower limb weakness, unsteady gait, impotence, weight loss of 6 kg in 3 months, skin darkening and hypertrichosis on both dorsal hands. He was admitted to our hospital in March 2001, and a nerve conduction velocity test and sural nerve biopsy confirmed demyelinating polyneuropathy. Serum and cerebrospinal fluid immunoelectrophoresis/immunofixation electrophoresis showed monoclonal gammopathy of IgG lambda. Bone marrow aspiration and biopsy revealed plasma cell myeloma. A bone survey revealed multiple opaque densities overlying the pubic bones, ischium and sacrum. Magnetic resonance imaging (MRI) showed osteosclerotic or blastic nodules and patches on the spine and pelvis; thus, osteosclerotic myeloma was suspected. Further laboratory examination of endocrine function revealed elevation of thyroid-stimulating hormone and adrenocorticoid hormone, and low levels of T4 and cortisol.

The patient received chemotherapy in the form of melphalan and prednisone between April 2001 and April 2003. In November 2004, he suffered recurrent bilateral pleural effusion and generalized oedema, and received DECP (dexamethasone, etoposide, cyclophosphamide, and cisplatin) chemotherapy between November 2004 and June 2005. Thalidomide (200 mg daily) had been administered for 7 weeks from September 2008 to combat aggravated pleural effusion exertional dyspnoea and bilateral oedema of the legs. From December 2008, the patient had been treated with bortezomib (1 mg/m²), on days 1, 5, 8 and 12 of a 3-week cycle, (repeated six times), plus prednisolone (at an initial dose of 40 mg per day, which was gradually tapered). Fluid overload and neurological deficit improved thereafter.

The patient visited our dermatology clinic in July 2009 with a tender erythematous plaque on his right calf that had developed several days previously. He reported that there had been a similar skin lesion on his left calf 3 months earlier, which was diagnosed as cellulitis and treated through repeated debridement and eventually covered with a split-thickness skin graft. Physical examination revealed many variously sized erythematous papules on the upper trunk – which had been diagnosed histologically as glomeruloid haemangioma – hypertrichosis on the dorsal hands, hyperpigmentation of the palms, and a 4 × 5 cm erythematous-to-violaceous plaque with irregular borders on the right calf (Fig. 1). A skin biopsy obtained from the right calf lesion revealed the presence of microthrombi and widespread calcification of the small-to-medium-sized blood vessels, consistent with a diagnosis of calciphylaxis (Fig. 2). The results of laboratory examinations, including a complete blood count, renal and liver function tests, measurements of electrolyte, fasting plasma glucose and intact parathyroid hormone levels, and assessments of autoimmune profiles, were all within normal limits or negative. The prothrombin time, activated partial thromboplastin time and protein C level were also within normal limits, while the protein S level was slightly decreased (72%; reference range: 75–130%). The lesion worsened, becoming necrotic and causing aggravated pain, and was thus debrided and later covered with a split-thickness skin graft. With no changes in concomitant drug treatment, the wound healed smoothly, and no new lesions were found in the next 4 months.



Fig. 1. (a, b) Multiple erythematous-to-violaceous papules, representing glomeruloid haemangioma, on the upper trunk. (c, d) A 4 × 5 cm erythematous-to-violaceous plaque with irregular borders on the right calf.

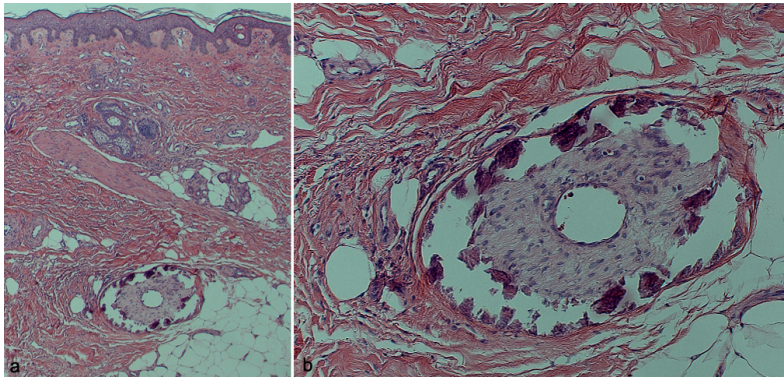


Fig. 2. (a) Acalcified vessel in the deep dermis (haematoxylin and eosin (H&E) $\times 40$). (b) Calcification of the blood vessel wall with intimal proliferation and thickening (H&E $\times 100$).

DISCUSSION

Dispenzieri (3) described the major and minor criteria for diagnosing POEMS syndrome. Our case fulfilled three major criteria (polyneuropathy, monoclonal plasma cell-proliferative disorder and sclerotic bone lesions) and three minor criteria (extravascular volume overload, endocrinopathy and skin changes). The pathogenesis of POEMS syndrome is not well understood, but elevation of pro-angiogenic and pro-inflammatory cytokines such as interleukin (IL)- 1β , tumour necrosis factor (TNF)- α , and IL-6 seems to play a role (4). Vascular endothelial growth factor (VEGF) is also thought to be a pathogenetic factor (5–7).

Calciphylaxis is generally associated with end-stage renal disease and hyperparathyroidism, but has also been linked with many other medical conditions (8). Its pathogenesis too remains unclear. Weenig et al. (9) integrated calciphylaxis risk factors with the molecular processes governing osseous and extra-osseous mineralization, and identified IL-1, TNF- α and IL-6 as candidate factors in vascular calcification. They also suggested the involvement of osteoblastic transformation in vascular smooth muscle cells, which has been reported to be induced by both TNF- α (10) and VEGF (11).

Korkmaz et al. (12) reported a case of calciphylaxis in a patient with rheumatoid arthritis, and proposed that prolonged corticosteroid use and decreased protein S levels are responsible for calciphylaxis in patients without renal failure or hyperparathyroidism. Our patient's long-term treatment with steroids and low protein S levels may have contributed to his vascular calcification and the formation of microthrombi in his blood vessels.

An association between osteoblastic activation and the treatment of multiple myeloma (MM) with bortezomib has been reported (13). Bortezomib combats increased expression of cytokines and angiogenic factors in MM (14) and has reported efficacy in POEMS syndrome (15, 16). Our patient developed calciphylaxis on his right calf after six courses of bortezomib treatment. Based on our case and the one reported by De Roma et al. (2), we suggest that the relationship between POEMS syndrome and calciphylaxis, and the pathogenesis of these two conditions, merit further study.

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