

A patient with POEMS syndrome responding to modified CyBorD chemotherapy as a bridge to autologous stem cell transplantation



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INTRODUCTION

We present a 49-year-old man with scleroderma-like skin changes who had recurrent ascites, hypogonadism, splenomegaly, and polyneuropathy. Serum studies found an IgA monoclonal gammopathy and an elevated vascular endothelial growth factor (VEGF). Imaging found sclerotic bone lesions, and a bone marrow biopsy found plasma cells. Given the constellation of findings, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome was diagnosed. Although profoundly debilitated at time of diagnosis, he improved rapidly with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) chemotherapy and, later, autologous peripheral blood stem cell transplantation.

CASE REPORT

A 49-year-old Tanzanian man with a history of chronic hepatitis B, hypogonadism, and hypothyroidism initially presented with a more than 10-year history of skin hyperpigmentation and tightening of his trunk, extremities, and fingers, greatly diminishing his range of motion. Review of symptoms was notable for weakness, myalgias, erectile dysfunction, depressed mood, weight loss, fatigue, night sweats, insomnia, shortness of breath, and paresthesias.

Examination found widespread indurated, hyperpigmented patches on the torso and extremities, with dermal and subcutaneous tightening and hair loss of

Abbreviations used:

CyBorD:	cyclophosphamide, bortezomib, and dexamethasone
POEMS:	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
SDH:	spontaneous subdural hemorrhage
VEGF:	vascular endothelial growth factor

the extremities (Fig 1). Tightening of the fingers was consistent with sclerodactyly (Fig 2).

Extensive rheumatologic serology workup was negative for autoimmune disease including antinuclear antibody, centromere, and Scl-70. A left anterior thigh wedge biopsy found crowded thick collagen bundles, partial loss of perieccrine adipose tissue, uneven epidermal pigmentation, and superficial perivascular lymphocytic infiltrate, suggestive of early scleroderma. No mucin was noted on colloidal iron stain.

Additional studies found mild restrictive lung disease and a small pericardial effusion. Computed topography of the chest, abdomen, and pelvis found thymic hyperplasia, splenomegaly, and sclerotic lesions of the spine, rib, and iliac bones.

The patient was initially evaluated at another center and treated with penicillamine for several years for the diagnosis of scleroderma. However, his skin tightening, pain, weight loss, and decreased mobility continued to progress, and he sought another opinion. We initially treated him with

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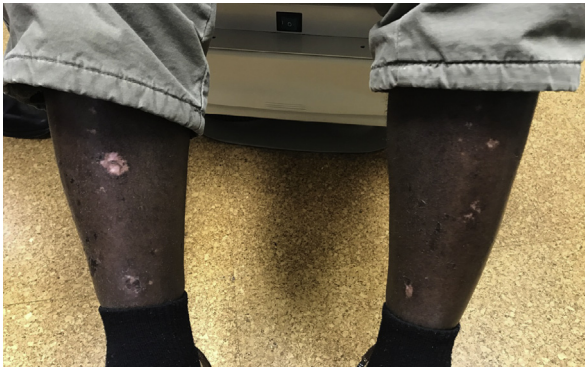


Fig 1. Bilateral lower extremities with generalized hyperpigmentation, skin induration, hair loss, and pink atrophic scars on the anterior shins.

methotrexate, which did improve skin thickening and pain. Soon thereafter he presented with severe frontal headache, vomiting, photophobia, and tinnitus, without history of head trauma. Imaging revealed bilateral subdural hematoma (SDH), requiring craniotomy. He rapidly recovered postoperatively. Six months later he developed new anemia and ascites. Paracentesis was consistent with portal hypertension, with a negative cytology and gram stain. Imaging failed to show cirrhosis or portal hypertension. Serum studies found newly elevated uric acid, elevated erythrocyte sedimentation rate, and leukopenia. Quantitative immunoglobulins showed a mildly elevated monoclonal IgA of 427 mg/dL (normal range, 70–400 mg/dL) and IgM of 270 mg/dL (normal range, 40–230 mg/dL). Serum immunofixation studies found only a faint IgA- λ band. There were no urine paraproteins detected. Chromogranin A was elevated at 1057 ng/mL (normal range, 0–95 ng/mL). Bone marrow biopsy found a mild increase in plasma cells (5%) with λ light chain excess.

Given suspicion for POEMS, a VEGF level was obtained and was found to be elevated at 287 pg/mL (range, 9–86 pg/mL); repeat level weeks later was 1517 pg/mL. Electromyography and nerve conduction studies found demyelinating/axonal neuropathy consistent with chronic inflammatory demyelinating polyneuropathy.

The patient was treated with 5 cycles of chemotherapy consisting of intravenous cyclophosphamide, 300 mg/m² orally on days 1, 8, and 15; oral dexamethasone, 40 mg on days 1, 8, and 15; and subcutaneous bortezomib, 1.5 mg on days 1, 8, and 15, on a 28-day cycle, a modification of the CyBorD regimen. He also received entecavir and acyclovir prophylaxis.

Within months, he no longer required paracentesis twice weekly and could walk comfortably

without significant stiffness or pain. He later underwent autologous peripheral blood stem cell transplantation with high-dose melphalan conditioning. At last follow-up, he was well and fully functioning, with continued improvement in skin hyperpigmentation and tightening. His only laboratory abnormality was mild thrombocytopenia.

DISCUSSION

POEMS syndrome is a paraneoplastic manifestation of a plasma cell disorder. Skin changes include hypertrichosis, glomeruloid hemangioma, clubbed nails, facial atrophy, dependent rubor with acrocyanosis, and sclerodermoid skin damages.¹ Skin biopsy may find basal layer hyperpigmentation, inflammation, and dermal fibrosis with intact adnexal structures, helping to differentiate it from scleroderma.² Neuropathy is often the predominant feature and is usually peripheral, ascending, and symmetrical, affecting both sensation and motor function. The most common endocrinopathies include hypogonadism, hypothyroidism, abnormalities in glucose metabolism, and adrenal insufficiency.

Diagnosis is sometimes elusive because of the low paraprotein level and minimal degree of plasma cell infiltration in bone marrow, usually comprising less than 5% of cells.² Some patients may have normal bone marrow biopsy results or have solitary or multiple plasmacytomas. The M-spike in patients with POEMS is typically IgA or IgG, minimal in size, and λ light chain restricted, as was the case here.

To our knowledge, SDH has not been reported in POEMS syndrome. In general, nontraumatic SDH is uncommon.³ Spontaneous subdural hemorrhage has been reported in a patient with scleroderma renal crisis⁴ and, recently, intraparenchymal hemorrhage was reported in a patient with POEMS and quasi-moyamoya syndrome.⁵ Perhaps because vascular abnormalities related to elevated VEGF levels could account for spontaneous hemorrhage, given the rarity of both nontraumatic SDH and POEMS, it is possible that the 2 conditions are related in this patient.

Because POEMS is a rare manifestation of a plasma cell disorder, patients with this condition are not typically included in trials of newer agents. As a result, older regimens once used for myeloma are often listed as first-line treatment for POEMS.⁶ We chose a treatment regimen including cyclophosphamide, bortezomib, and dexamethasone.⁷ We considered autologous transplantation (efficacious in amyloidosis as initial treatment), but the literature suggests a high incidence of engraftment syndrome among POEMS patients.⁸ This finding is probably because POEMS patients have abnormal cytokine



Fig 2. **A**, The patient's dorsal hand before development of POEMS syndrome. **B**, Dorsal hands with circumferential tightening of the fingers, subungual pallor, and noteworthy hypertrichosis.

levels that have not resolved by time of engraftment, despite effective high-dose chemotherapy. For this reason, and because our patient was extremely debilitated, a multidisciplinary team consisting of dermatology, rheumatology, and oncology elected to treat him with a modification of CyBorD.⁹ Since then, a series of patients successfully treated with this regimen has been reported.¹⁰

We believe this patient's history supports the notion that CyBorD is both safe and effective in POEMS syndrome. Of note, although this patient had severe neuropathy, the clinical benefit of disease control outweighed possible toxicity from bortezomib. We believe that any drug effective in myeloma may possibly be effective in POEMS syndrome, but until safety is demonstrated (especially regarding the risk of cytokine-mediated reactions that might occur with monoclonal antibodies or immunotherapy) we believe a regimen including cyclophosphamide, bortezomib, and dexamethasone may be considered for the initial treatment of POEMS syndrome.

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