case report

Autologous peripheral blood stem cell transplantation in a patient with POEMS syndrome

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POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome, also known as osteosclerotic myeloma, Craw-Fukase syndrome, or Takasuki syndrome, is a rare paraneoplastic syndrome caused by an underlying plasmaproliferative disorder with multiorgan involvement due to capillary leak syndrome and thromoembolic events, resulting in a poor prognosis.[1-3] Consistent plasma cell disorders include a monoclonal component, often in small quantities with a lambda light chain isotype, and plasmacytoma, often solitary lesions. The pathogenesis of POEMS syndrome is not well understood, but overproduction of vascular endothelial growth factor (VEGF), probably secreted by plasmacytoma, may be responsible for most of its characteristic symptoms.[4] Treatment depends on specific characteristics of the disease and the patient (radiation therapy for plasmocytoma, autologous bone marrow transplantation in young subjects, corticosteroid therapy or chemotherapy in the elderly). The usefulness of thalidomide and bevacuzimab in refractory POEMS syndromes remains to be seen.[4,5] Most cases reports and series have described patients from Japon,[6] China,[7] and India.[8] POEMS syndrome is rarely reported in Latin America,[9-12] and then mostly in the form of case reports. This case, a Colombian male, is probably the first transplanted patient with POEMS syndrome on this continent.

CASE

A 44-year-old Colombian male was admitted on January 2004 for lumbar pain, paresthesias, and lower limb weakness for 10 months. He was referred for an increase in abdominal girth and moderate dyspnea in recent weeks. He smoked and consumed liquor occasionally, and had no history of exposure to toxic substances or a family history of neurological disease. Physical examination displayed alteration of proprioception and tactile sensitivity in the lower extremities, widespread arreflexia, muscle strength 4/5 in all segments, edema in the lower extremities, and white nails and clubbing, without splenomegaly. Laboratory results included CBC with thrombocytosis (571×10^9/L), C-reactive protein of19 mg/L, TSH of 17.2 mIU/mL, low levels of vitamin B12 (130 pmol/L) and hypoalbuminemia (34 g/L). Hepatic and renal function, and electrolytes, including calcium, were normal. A lumbar puncture showed increased protein (1.52 g/L), without cells or bacteria. Studies for HIV, HTLV1, hepatitis B and C were negative, as were studies for autoimmunity. The protein electrophoresis showed a modest monoclonal gamma peak. A spinal CT scan showed only slight protrusion of the L5-S1, which did not explain neurological symptoms. He had an abdominal CT scan that evinced bilateral pleural effusion and ascites, without splenomegaly or hepatomegaly. The electromyography in four limbs demonstrated sensory-motor demyelinating polyneuropathy with dominance in the lower limbs. He was discharged with treatment for hypothyroidism and vitamin B12 deficiency.

Seven months later he was assessed in the Endocrinology Outpatient Service. He had lost 10 kilograms of weight. The weakness had progressed and he was unable to climb scales, hold objects in his hands or stand unaided. Physical examination revealed widespread hyperpigmentation and a decrease in pubic hair. Orthostatic hypotension was found, and measurement of cortisol (71.7 nmol/L) confirmed the diagnosis of adrenal insufficiency. Polyendocrinopathy syndrome was diagnosed and treatment with prednisone and fludrocortisone was started.

Twenty months after first consultation he was admitted by the emergency department for anasarca that compromised his breathing. On immunofixation electrophoresis an IgG lambda monoclonal peak was

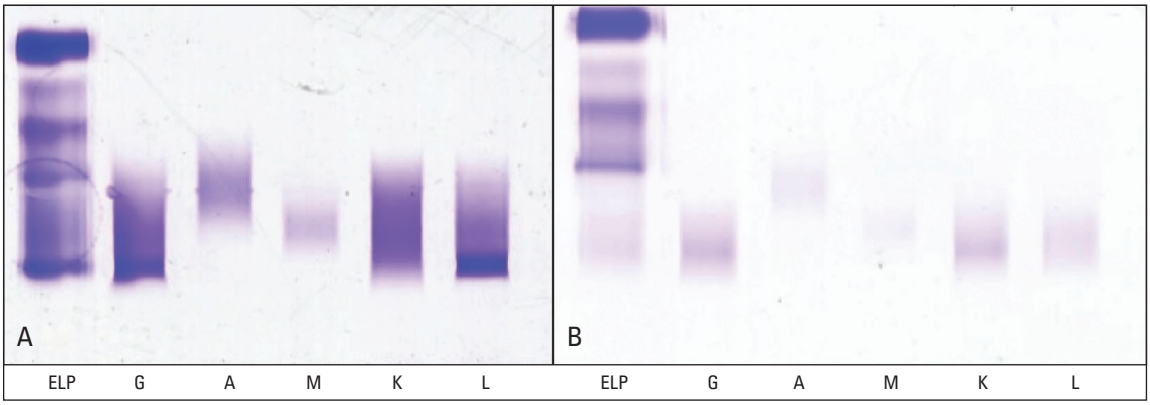

Figure 1. Immunofixation at time of diagnosis (A) and 26 months after the APBSCT (B).

detected (Figure 1A) with immunoglobulin levels of IgA: 0.297 g/L, IgG: 2.237 g/L and IgM: 0.178 g/L. Bence-Jones protein and cryoglobulins were negative. Echocardiography ruled out pulmonary hypertension and spirometry revealed a restrictive pattern: FVC of 2.25 L (67% of predicted), FEV1 of 1.8 L (65% of predicted), and FEV1/FVC of 81. POEMS syndrome was diagnosed based on the following criteria: polyneuropathy, monoclonal gammopathy IgG lambda, hypothyroidism, adrenal failure, skin changes, extravascular overload (edema, ascites and pleural effusions), clubbing and white nails. He had no organomegaly, osteolytic or osteosclerotic lesions. A bone marrow study showed mild increased plasma cells. We started treatment with prednisone plus melphalan, levothyroxine, and vitamin B12. He was scheduled for high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (APBSCT).

Six months after diagnosis he was conditioned with melphalan 200 mg/m^2 and two autologous non-cryopreserved[13] G-CSF mobilized bags were infused containing 8.2×10^6 CD34/kg. He had a culture fever, with mild CRP elevation occurring on day +10, for which he received broad-spectrum antibiotic coverage. On day +5 we started G-CSF until sustained engraftment, which occurred on day +14 and he was discharged on day +22. Thirty months after the transplant the patient was totally autonomous, his neurological symptoms had completely improved and electromyography showed signs of active remyelinization. He had no edema, immunoelectrophresis was normal (Figure 1B) and spirometry showed significant lung function improvement: FVC of 2.9 L (83% of predicted), FEV1 of 2.17 L (73% of predicted) and FEV1/FVC of 73.1.

DISCUSSION

The diagnosis of Crow-Fukase syndrome is based on the presence of chronic sensori-motor polyneuropathy along with other characteristic generalized symptoms denoted by the acronym POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes). Other features not initially described include elevated levels of vascular endothelial growth factor, sclerotic bone lesions, Castleman disease, papilledema, extravascular volume overload, thrombocytosis, polycythemia, fatigue and clubbing.[5] Historically, therapies for POEMS syndrome have included radiation, alkylator-based therapies and steroids, but in recent years the arsenal of treatments has expanded to include thalidomide, lenalidomide, high doses of melphalan with APBSCT and more recently the anti-vascular endothelial growth factor (VEGF) antibodies (bevacizumab) with controversial results.[14-16] Treatments with thalidomide or lenalidomide, and anti-VEGF monoclonal antibody (bevacizumab) should be considered as future therapies. Experience has shown that APBSCT is an effective therapy, with response rates above 90% although patients with POEMS syndrome seem to have a high risk for an engraftment-type syndrome with high morbidity.[17]

Our patient had severe disability secondary to the syndrome and was successfully treated with APBSCT. His transplant course was relatively unremarkable in that he did not develop engraftment syndrome and most importantly, remained asymptomatic 30 months after the transplant. There are no other reported cases of stem cell transplantation for treatment of POEMS syndrome in Latin America.

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