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Male aged 31 years with polyneuropathy, prostration and hypogonadism

Antonio F. del Río Prado, Alfredo A. Reza Albarrán and Francisco Javier Gómez Pérez*
Department of Endocrinology and Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, D.F., México

Abstract

We present the case of a 31 year-old male patient, who presented polyneuropathy, symmetrical, ascending, and progressive, that led to prostration of eight months duration, accompanied by hypogonadism, hypothyroidism, hyperprolactinemia, and the presence of multiple erythematous nodules on the skin. The MRI showed hypointense lesions in the vertebrae T-6 and L-4 with sclerotic appearance. The bone marrow biopsy reported the presence of 12% plasma cells with λ restriction, supporting monoclonal gammopathy (plasmocytoma). (Gac Med Mex. 2015;151:240-3)
Corresponding author: *Antonio F. del Rio Prado, tdelrio@hotmail.com*

KEY WORDS: *Polyneuropathy. Hypogonadism. Monoclonal gammopathy.*

Case description

This is the case of a 31-year old male, construction worker, with no relevant medical or personal history.

Current complaint

In August 2011, he experienced bilateral back pain of five days' evolution, with 8/10 intensity, without irradiations or exacerbating factors and that was ameliorated by rest. Subsequently, he developed unstable gait, paresthesias and decreased sensitivity from both feet plants to the ankles. In November 2011, the patient was hospitalized due to an arterial hypertension event (180/120 mm Hg), edema and dyspnea, which required treatment (50 mg oral [PO] hydrochlorothiazide every 24 h and 100 mg losartan PO every 24 h). He presented ascending and symmetric progression of paresis, as well as decreased strength, initially in the toes and then, as foot drop; erectile dysfunction was added up, which exacerbated over the next few months. In January 2012, the patient experienced paresthesia in both feet, reaching the calves and associated with headache and blurry vision events. In April 2002, a decrease in strength and sensitivity up to the knees started to develop, with subsequent progression to the pelvic region and prostration, as well as onset of urinary and defecation urgency. The patient referred having lost 20 kg over the past 10 months.

He was admitted to the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán with blood pressure of 140/90 mm Hg, HR of 100 bpm, RR of 20 per minute, temperature of 36.5 °C and presence of an erythematous nodule of approximately 0.5 x 1 cm on the right shoulder, hyperchromic maculae in the back

Correspondence:
*Antonio F. del Rio Prado
Departamento de Endocrinología y Metabolismo
Instituto Nacional de Ciencias Médicas
y Nutrición Salvador Zubirán
Vasco de Quiroga, 15,
Col. Sección XVI, Del. Tlalpan, C.P. 14000, México, D.F., México
E-mail: tdelrio@hotmail.com

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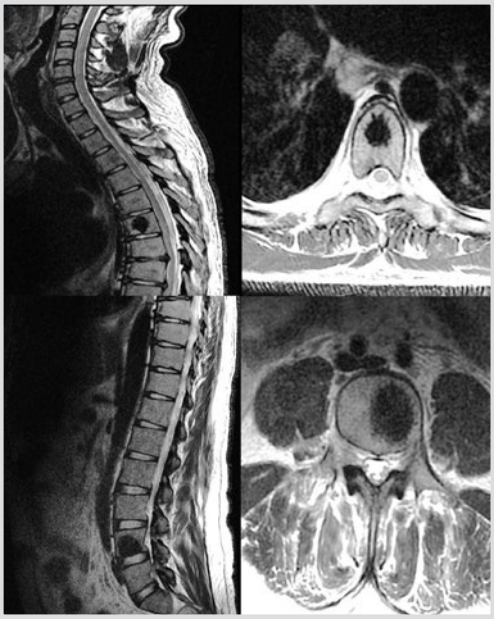

Figure 1. *Magnetic resonance imaging of the dorsal and lumbar spine showing hypointense zones in T-6 and L-4, suggestive of osteosclerotic lesions.*

and the palmo-plantar areas, a bilateral papilledema, drumstick fingers and strength decrease in lower extemities (4/5) and feet (2/5), MSR (0/4), decreased sensitivity to pain and temperature with sensitivity level in T11.

The laboratory tests revealed the following relevant data: WBC: 7.200; Hb: 12.2 g/dl; hematocrit: 37.2%; platelets: 306.000; glucose: 77 mg/dl; creatinine: 1.56 mg/dl; urinalysis with proteinuria of 1 g/l, hemoglobin ++ and 24-h total protein of 640 mg/dl. In addition, the patient tested HIV (–), VDRL (–) and hepatitis viral profile (–).

Magnetic resonance showed no data consistent with endocranial hypertension. Lumbar puncture: acellular, pH: 7.4, glucose: 63 mg/dl (serum: 93 mg/dl), protein: 222 mg/dl, Ac: C. Neoformans and pneumococcus (–), cultures with no development. Dorsolumbar magnetic resonance showed a bone lesion in T-6 and L-4 with osteosclerotic appearance (Fig. 1), and abdominal ultrasound revealed the presence of nephromegaly, hepatomegaly and splenomegaly. The nerve conduction velocity test showed axonal sensitive and motor polyneuropathy with predominance in lower extremities. Surgical resection of the right shoulder nodular lesion was performed, with histopathological report of glomeruloid hemangioma (Fig. 2). The echocardiogram revealed a slight dilation of the right cavities, mild tricuspid

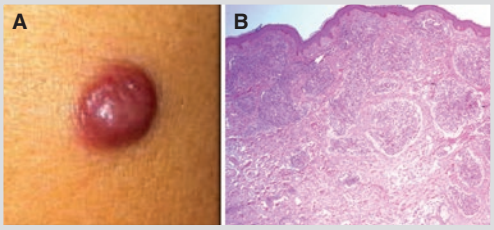

Figure 2. A: *glomeruloid hemangioma.* **B:** *histopathology with presence of nodular lesions in superficial and deep dermis.*

insufficiency, serious pulmonary hypertension (sPAP: 70 mm Hg), borderline left ventricular function (LVEF: 55%), with mild restrictive pattern in respiratory tests. With regard to endocrine parameters, the thyroid profile showed data consistent with mild primary hypothyroidism with negative anti-thyroid antibodies plus secondary hyperprolactinemia (Table 1) and data of central hypogonadism, possibly hypothalamic (Table 2). Protein electrophoresis was performed (normal), as well as serum immunofixation, with a slight monoclonal pattern in the IgA-l chain, Bence Jones protein negative and electrophoresis in urine with no monoclonal peak. Bone marrow aspiration and biopsy showed 8% of plasma cells with hypercellularity and vertebral bodies (T-6 and L-4) biopsy reported 12% of plasma cells with l chains restriction, consistent with plasmacytoma (Fig. 3).

Table 1. Hormone profile

Hormone profile	Values	Reference
Cortisol am	7.74 ug/dl	6.7-22
ACTH	54 pg/ml	10-100
FSH	6.09 mU/ml	1.24-19.26
LH	10.38 mU/ml	1.27-19.26
Testosterone	0.5 ng/dl	1.75-7.81
Prolactin	39.08 ng/ml	6-29
T3 uptake	47.2%	32-48
Total T3	0.64 nmol/l	1.34-2.73
Total T4	84.56 nmol/l	78.3-157.4
TSH	7.23 µIU/ml	0.34-5.60
Thyroglobulin	22.42 ng/ml	< 35
Antibodies	Negative TPO and Tg*	

*Peroxidase and thyroglobulin antibodies.

Table 2. GnRH-LH test

–15 min	8:35 am	10.23 mU/ml
0	8:50 am	9.65 mU/ml
15 min	9:05 am	19.28 mU/ml
30 min	9:20 am	34.90 mU/ml
45 min	9:35 am	38.43 mU/ml
60 min	9:50 am	48.36 mU/ml
90 min	10:20 am	49.82 mU/ml
120 min	10:50 am	

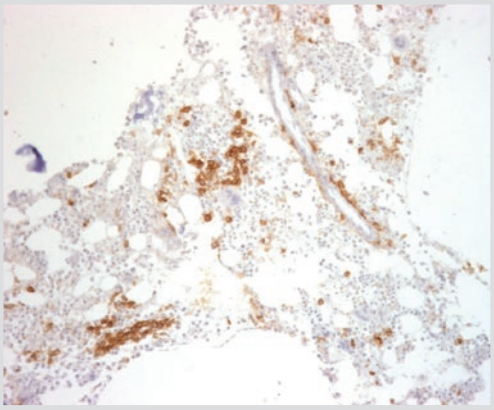

Figure 3. *L-4 vertebra biopsy with CD 138 staining, with presence of plasma cells in the bone marrow.*

Discussion

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare disease, with a prevalence of 0.3 per 100,000 inhabitants. For a long time, there have been only reports of isolated cases, later grouped in a few clinical series in Japan, France and the Mayo Clinic in the USA[1]. Frequently, there is a delay in diagnosis, and the first manifestation is often polyneuropathy. A higher prevalence is recognized in males, preferable between the sixth and the seventh decades of life. The course of the disease is chronic and survival is about 4-fold greater than in patients with classical myeloma multiple[2].

POEMS syndrome pathogenesis is not known. It has been attributed to the role of several pro-inflammatory cytokines with elevated levels of interleukin 1b, interleukin 6 and tumor necrosis factor[3]. An etiologic role of human herpesvirus 8 has been implied, with 78% of patients reported with POEMS associated with Castleman disease and 22% with isolated POEMS. However, the main pathogenic role currently involved is for the vascular endothelial growth factor (VEGF-1), which induces an increase in vascular permeability and is considered to be important in the angiogenesis process, which facilitates the occurrence of ascites, edema, organomegaly, cutaneous hemangiomas and also neuropathy due to alteration of the blood-nerve barrier[4]. VEGF-1 is thought to increase its levels in POEMS syndrome by increased production at the platelet and plasma cell level. A high prevalence of λ chains has been found (> 95% of cases), which take part in the pathogenesis of the disease.

Table 3. POEMS syndrome diagnostic criteria

Major criteria (mandatory)	– Polyneuropathy (typically demyelinating) – Monoclonal plasma cell (mostly l) proliferative disorder
Other major critera (only one required)	– Castleman disease – Osteosclerotic lesions – VEGF levels elevation
Minor criteria	– Organomegaly (splenomegaly, hepatomegaly or lymphadenopathy) – Hypervolemia (edema, pleural effusion, ascites) – Endocrinopathy (adrenal, thyroid, hypophysiary, gonadal, parathyroid, pancreatic) – Cutaneous changes (hyperpigmentation, hypertrichosis, plethora, glomeruloid hemangioma) – Papilledema – Thrombocytopenia and polycytemia
Other signs and symptoms	– Acropachy, weight loss, hyperhidrosis, pulmonary restrictive disease, thrombotic diathesis, diarrhea, vitamin B12 deficiency, joint pains, pulmonary hypertension, hyperproteinorachy

Endocrinopathy is a central characteristic of the POEMS syndrome[5]. Multiple hormone disorders have been described, including hypogonadism, diabetes mellitus (DM), hypothyroidism, hyperprolactinemia, adrenal insufficiency, gynecomastia, erectile dysfunction and hypoparathyroidism. The cause of endocrinopathies is unknown. No circulating antibodies against hormones or specific hormone receptors have been found. Studies in autopsies of endocrine organs have been normal.

VEGF-1 plays a critical role in angiogenesis. It has been hypothesized that VEGF overexpression in POEMS syndrome might affect endocrine axes due to alterations in the balance of angiogenic factors participating in hormone regulation and endocrine gland secretion.Currently, there is no consensus with regard to treatment. In limited lesions, radiotherapy and surgical resection have shown good results, with substantial improvement of neuropathy[6]. When lesions are extensive, multiple systemic therapies have been tried, with plasmapheresis and immunoglobulin proven ineffective[7]. Standard or high-dose chemotherapy wlth autologous hematopoietic cell transplantation has shown to be effective[8]

Treatment with melphalan and dexamethasone was beneficial, improving survival and decreasing symptoms, but with associated risk of myelodysplasia and acute leukemia[9]. There are new therapies that appear to be promising for the management of the POEMS syndrome, such as thalidomide, lenalidomide and bortezomib, but further studies are required to consider their effectiveness[10].

Our patient was started on pharmacological management with high doses of dexamethasone and cyclophosphamide (12 cycles) and is in a transplantation protocol, only with thyroid hormone replacement (75 µg/day) and intramuscular testosterone (250 µg) every 3 weeks, which has markedly improved neuropathy, dermal lesions and hormone profile.

Conclusion

The POEMS syndrome is an important paraneoplastic syndrome associated with a plasma cell clonal neoplasm. Establishing the diagnosis is challenging, but with a good history and physical examination, in addition to an appropriate radiological assesment, measurement of VEGF levels and careful analysis of bone marrow, this syndrome can be differentiated from other conditions. There is high prevalence of endocrinopathies in the POEMS syndrome and, therefore, hormonal disorders occurring during the disease should be monitored and treated.

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