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Case Report
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# Is a severe and early neuropathy related to bortezomib? Is it related to the treatment response?

## Abstract

Myeloma is characterized by the neoplastic proliferation of a clone of plasma cells that invades the bone, causes destruction of the skeleton, and causes bone pain and fractures. In addition, other important features are anemia, hypercalcemia and renal failure. The standard treatment in Spain for autologous stem cell transplant (ASCT)-eligible patients is VTD (bortezomib, thalidomide, dexamethasone). Both bortezomib and thalidomide can cause or exacerbate an existing neuropathy. The mechanism by which they produce it is different in the two drugs.[1]

A 52-year-old white male was referred to our hospital for the evaluation of anemia (12 g/dL) and serum monoclonal protein (>4 g/dL). The diagnosis was a high cytogenetic risk MM stage R-ISS IIIA, without bone lesions. He only presented mild anemia. He started treatment with standard doses and in accordance to the usual protocol in a candidate patient for autologous stem cell transplant, based on a thalidomide and bortezomib scheme.

On the 15th day of the 2nd cycle, the patient showed an autonomic neuropathy and an affectation of the deep sensibility, predominantly the vibratory and proprioceptive with generalized muscle weakness predominant in the lower limbs. He had no pain. He was totally dependent for the basic activities of daily life. Regarding the MM response, the patient showed a strict complete response.

This case illustrates a young man with a high cytogenetic risk MM who developed an acute and early polyneuropathy grade IV after 1.5 cycles of standard treatment and with myeloma in strict complete response. The remarkable aspect about this case is the severe and early neuropathy, and an early, deep and persistent myeloma response. On some occasions this relationship has been reported, and we report an example of it.

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## Background

Multiple myeloma (MM) is the second most frequent hematologic disease. Myeloma is characterized by the neoplastic proliferation of a clone of plasma cells that in most cases produces a monoclonal protein. This proliferation in the bone marrow frequently invades the bone, causes destruction of the skeleton, and causes bone pain and fractures. In addition, other important features are anemia, hypercalcemia and renal failure. The standard treatment in Spain for autologous stem cell transplant (ASCT)-eligible patients is VTD (bortezomib, thalidomide, dexamethasone). Both bortezomib and thalidomide can cause or exacerbate an existing neuropathy. The mechanism by which they produce it is different in the two drugs.[1] The remarkable thing about this case is the severe and early neuropathy, and an early, deep and persistent myeloma response. On some occasions this relationship has been reported, and we report an example of it.

## Case report

A 52-year-old white male was referred to our hospital for the evaluation of anemia (12 g/dL) and serum monoclonal protein (>4 g/dL). The patient had no major complaints. He had no pain or relevant diseases. He was not taking any treatment at home. He was cycling in his leisure time.

### In the initial exam

His physical examination was unremarkable. He had an athletic body. There were no data of chronic liver disease. In his cardiac auscultation, there were no murmurs and in his pulmonary auscultation, the respiratory noises were normal. In the abdominal examination, there were no masses or visceromegalies. He had no palpable lymph nodes. There were no edemas in his lower limbs. His cranial nerves were explored without alterations. The reflexes were not altered, and the rest of the neurological exams were normal.

The other laboratory values were normal but the protein study showed: total proteins 11.0 g/dL, serum albumin 3.1 g/dL, and IgG 4622 mg/dL, IgA 18.0 mg/dL, IgM 19.0 mg/dL, Free light Kappa chains 1.3 mg/L, Lambda 282.5 mg/L with a serum monoclonal band IgG Lambda of 4.04 g/dL. In urine, the protein excretion was 352 mg/24h with Bence Jones (B-J) proteinuria positive and a monoclonal Lambda - free band.

A bone marrow aspirate and biopsy revealed ≥60% clonal plasma cells. His genetics revealed 88% plasma cells with t(14; 16) and 71% presented gain of 1q.[2] The PET / CT performed before treatment did not describe captures or bone lytic lesions.

After diagnosis of high cytogenetic risk MM, stage R-ISS (Revised International Staging System)[3] IIIA, the patient initiated treatment according to the protocol Rosiñol colleagues of 2012, standard in Spain for ASCT-Eligible Patients:[4] Bortezomib (V) 1.3 mg/m2 SC once per day on days 1, 4, 8, 11; Thalidomide (T): cycle 1: 50 mg PO once per day on days 1 to 14, then 100 mg PO once per day on days 15 to 28 and cycles 2 to 6: 200 mg PO once per day on days 1 to 28 and Dexamethasone (D) (28-day cycle for 6 cycles of VTD).

In the first control (1st cycle), the patient presented orthostatic dizziness, distal paresthesia in lower limbs, xerostomia and difficulty

in swallowing. He had no pain. On the whole, PN was assessed as grade 1-2 neuropathy so the doses of the protocol were maintained. He had a partial response,[5] with immunoglobulin G 1070 mg/dL and Free light Lambda chains of 45.6 mg/L. his hemoglobin was 14.5 g/dL and albumin 2.4 g/dL. In this control, urine M-protein level was not measured. On the 15th day of the 2nd cycle, the patient presented loss of strength in the lower limbs with gait disturbance, urination difficulty and diarrhea. No lumbar pain.

In his physical examination, the patient presented xerostomia, bladder balloon. He had generalized muscle weakness, predominantly in the lower limbs, with areflexia and impaired standing balance. He had affectation of proprioceptive and vibratory sensitivity. No shivering. No pain.

Laboratory data showed no hydrolectrolytic alterations or renal insufficiency. The study of cerebrospinal fluid, showed no infection or infiltration by MM. MRI of the spine showed no stenosis of the spinal canal or bone damage.

His electroneuromyography revealed motor axonal involvement, predominantly in the lower limbs, chronic neurogenic compromise in left L4 and L5 territories without active denervation and loss of motor units in other explored territories. Somatosensory evoked potentials in lower limbs showed significant delay in posterior cord conduction. His neurographyc exploration was compatible with a sensory-motor polyneuropathy of axonal characteristics and of clear sensory predominance, of upper and lower extremities.

Regarding the MM response, the patient showed a strict complete response:[5] there were no monoclonal bands in serum or urine. No aberrant plasma cells were detected in the BM aspirate, and there was no measurable residual disease in the flow cytometry ($<1/10^5$).

The patient showed an early, severe autonomic neuropathy and an affectation of the deep sensibility, predominantly the vibratory and proprioceptive, with areflexia. During his hospital admission he developed a generalized amyotrophy. He was totally dependent for the basic activities of daily life. He did not have any pain. He achieved a slow progressive improvement with rehabilitation and physiotherapy but standing up and walking was not possible. Partial recovery of vibrational sensitivity was achieved but maintained proprioceptive sensitivity abolished.

After two and a half months without treatment, the revaluation of MM still showed a strict complete response,[5] and it was decided to consolidate the MM response with autologous hematopoietic cell transplantation, with melfalan 200, without significant incidents. Currently, 8 months after this, with rehabilitation and physiotherapy he can walk with help, but the improvement is slow and his hands are still affected by sensitive neuropathy.

Bortezomib-induced PN (BIPN) typically occurs within the first treatment cycles. It is a sensory PN (pain, paresthesia, burning sensation, dysesthesia, numbness, sensory loss) affecting the feet more than the hands. Patients may present a suppression/reduction in their deep tendon reflexes in proportion to sensory loss in proprioception and vibratory sensitivity. The nerve conduction study reveals low amplitude of sensory action potentials, in keeping with a sensory, axonal polyneuropathy, with predominant small fiber involvement. Motor impairment is rare.[1,6]

Thalidomide is an immunomodulatory drug (IMiD) and neurological complications usually occur after prolonged exposure.[7] The PN includes bilateral and symmetrical sensory disorders, rarely motor disorders or dysautonomia. Patients may experience stinging sensations or numbness (distal paresthesia and hyperesthesia) that initially affect the toes. Trembling is very common. Later, the vibrational sensitivity and proprioception may be affected. Motor impairment is rare. The electrophysiological study shows a length-dependent axonal neuropathy.[1,6]

## Summary

In summary, a young man with a high cytogenetic risk MM who developed an early and acute polyneuropathy grade IV[8,9](sensory-motor axonal characteristics, and clear sensitive predominance) after 1.5 cycles of standard treatment and with myeloma in strict complete response.

The most characteristic aspects were the rapid establishment of a very limiting PN, the main autonomic affectation and the loss of proprioceptive and vibrational sensitivity, without pain. But it is important to highlight and relate this toxicity to the rapid and deep response of MM.[10]

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## Conflicts of interest

The author declares no conflicts of interest.

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