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CLINICAL CASE

Bilingual edition English/Spanish

Guillain-Barré syndrome of a patient under bortezomib treatment

Síndrome de Guillain-Barré en un paciente en tratamiento con bortezomib

María Mar Herráez-Albendea¹, Almudena Amorós-Paredes²,
Marta Arteta-Jiménez²

¹Hematology and Hemotherapy Service, Hospital Santa Bárbara, Puertollano, Ciudad Real. Spain. ²Pharmacy Service, Hospital Santa Bárbara, Puertollano, Ciudad Real. Spain.

Author of correspondence

María Mar Herráez-Albendea
C/ Julio Palacios, 29, escalera B,
planta 13, puerta D
28029, Madrid, Spain.

Email:
marherraez@gmail.com

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Introduction

Guillain-Barré Syndrome (GBS) is an autoimmune polyradiculoneuropathy that affects the peripheral nerves and nerve roots, presenting itself as a flaccid, ascending reflux paralysis, which can cause respiratory failure and death. This can be reversed if the cause is known and an early diagnosis is made. There are recognized triggers such as infections, vaccines, neoplastic processes, pregnancy and surgery. However, the ratio with drugs such as bortezomib has occasionally been included in the literature as an event prior to the occurrence of said entity^{1,2}.

Bortezomib is a reversible proteasome inhibitor drug indicated for either monotherapy or combined therapy in the treatment of newly diagnosed multiple myeloma (MM) adult patients, as well as refractory or relapsing patients and in mantle cell lymphoma. Proteasome inhibition alters the regulatory proteins that control the progression of the cell cycle causing its arrest and apoptosis³. The most reported side effect by using this drug affects the gastrointestinal system, others are weakness, peripheral neuropathy and decreased platelet count—frequent manifestations that can occur in monotherapy or in combination—. This paper describes the case of a patient diagnosed with MM IgA Kappa International Staging System (ISS) -Stage II, Durie-Salmon Stage (DS) II-A with secondary amyloidosis and cardiac and renal involvement under bortezomib-lenalidomide-dexamethasone⁴ (VRD) therapy, developing GBS in the course of treatment.

Case description

Seventy-seven-year-old woman with a personal history of arterial hypertension on olmesartan medoxomil 20 mg/amlodipine 5 mg every 24 hours, diagnosed with MM IgA-Kappa with secondary amyloidosis and cardiac and renal involvement on VRD treatment, adjusted at the beginning of each cycle according to creatinine clearance and hematological values (bortezomib 1.3 mg/m²/subcutaneous on days +1, +4, +8 and +11 of each cycle, lenalidomide 10 mg orally/day from day +1 to day +21 of each cycle and dexamethasone 20 mg/oral from day +1 to day +4 and from day +9 to day +12 of each cycle). On the +8 day of the second cycle, the patient reported an accidental fall as well as clamping and weakness of both lower limbs, of proximal predominance, not associated with loss of consciousness, sphincter relaxation or other symptoms. The neurological examination revealed aquileia and patellar reflexes, not developing autonomic alterations or loss of sensation. The analytical study showed leukocytes 3,600 mm³, neutrophils 1,400/mm³, platelets 93,000 mm³, creatinine 1.6 mg/dL (glomerular filtration estimate of 33.06 mL/min), β_2 -microglobulin 5 mg/L, while the remaining parameters were normal. A lumbar puncture was performed observing albumino/cytological dissociation (proteins 2.58 g/L, leukocytes 0, glucose 53 mg/dL). This resulted in Gram staining and negative cultures, ruling out the presence of malignant cells in the histopathologic study. Electrophysiological studies showed decreased motor conduction velocities in

KEYWORDS

Multiple myeloma; Guillain-Barre syndrome; Bortezomib;
Neuropathy; Adverse reactions.

PALABRAS CLAVE

Mieloma múltiple; Síndrome de Guillain-Barré; Bortezomib;
Neuropatía; Efectos adversos.



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the peripheral nerves of lower limbs, with normal amplitude and prolongation of distal latencies. The electromyogram described neurogenic traces of diminished amplitude with intense partial loss of motor unit potentials of the big toe's and abductor muscles—with no spontaneous denervation activity—, as well as neurogenic traces of diminished amplitude and intense motor unit potentials partial loss in the quadriceps muscle, with no spontaneous denervation activity. A nuclear magnetic resonance was performed observing signs of chronic ischemic microangiopathy.

The patient was diagnosed with GBS, bortezomib treatments was immediately stopped due to neurotoxic complications clearly established with this drug. Thus, the administration of intravenous immunoglobulin 0.4 g/kg/day for five days was initiated, resulting in a complete clinical recovery and maintaining the remaining therapeutic scheme—since a progressive improvement of the neurological symptomatology was observed after the suspension of bortezomib—.

Discussion

Bortezomib is a proteasome inhibitor widely used in the MM treatment, as well as in mantle cell lymphoma. The neurotoxic effects induced by bortezomib and lenalidomide are very variable. In some cases, they are confused with neurological diseases or with progression of their hematological disease. Symptoms may appear after the first doses or months after treatment. However, even though the majority of patients who develop them do not present an immediate risk, they should be carefully evaluated. Serious cases of bortezomib-induced neurotoxicity have been reported, such as cerebral edema, transient ischemic accident, coma, imbalance of the autonomic nervous system, autonomic neuropathy, and even psychomotor hyperactivity, among others, the latter being considered as rare adverse effects.

GBS is an acute autoimmune polyradiculoneuropathy that affects the spinal cord's peripheral nerves and nerve roots. The patient developed

the symptomatology on day +8 of the second cycle of the VRD scheme, with no other precipitating factors such as infections, vaccines, neoplastic processes, pregnancy or surgery. The symptoms that allowed us to suspect the diagnosis of GBS were distal weakness and developed dysflexia, along with neurophysiological signs and cerebrospinal fluid alteration^{5,6}. Clinical improvement after discontinuation of the drug and receiving treatment with immunoglobulins suggests an effect associated with this complication. The temporal ratio between the use of bortezomib and the developed symptomatology in the described case maintaining lenalidomide seems to be a very suggestive causal link between both^{7,8}.

The case presented and the scarce published literature indicate that, although this adverse effect is not included in the summary product characteristics, GBS is a possible potentially serious side effect with a high morbidity and mortality rate, since it may occur during the course of bortezomib treatment. Therefore, attention should be paid to this complication, as reported in the literature, such as the case published in 2015 by Dai *et al.* and in 2019 by Xu *et al.* It is considered important to take into account the differential diagnosis of neuropathies, so that an appropriate diagnosis and treatment can be established as early as possible. In this case, MM could be a risk factor for the development of GBS induced by bortezomib. In conclusion, although it is a rare adverse effect, the association of GBS induced by bortezomib should be considered, even after the first treatment cycle. This case has been notified to the Pharmacovigilance Center of Castilla-La Mancha.

Founding

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Conflict of interest

No conflict of interests.

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