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Bortezomib-induced neuropathy in multiple myeloma manifesting as foot drop due to peroneal nerve palsy

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SUMMARY

We present the case of a man in his 50s with multiple myeloma who developed foot drop after receiving bortezomib-dexamethasone combination chemotherapy. Diagnostic evaluations, including haematological parameters, nerve conduction studies and imaging, were performed to confirm the diagnosis and assess the extent of neuropathy. He was managed conservatively with analgesics and vitamin supplements, and bortezomib was temporarily withheld. The neuropathy gradually improved, and bortezomib was successfully reintroduced without recurrence of foot drop. Bortezomib-induced foot drop is a rare complication of bortezomib-based therapy in patients with multiple myeloma. Early recognition and intervention are crucial to minimise impact on quality of life. This case report emphasises the safe reintroduction of bortezomib post-neuropathy resolution, emphasising the importance of early recognition and multidisciplinary management.

BACKGROUND

Bortezomib is a proteasome inhibitor used in treating multiple myeloma, a haematological disease characterised by clonal proliferation of plasma cells.[1] Bortezomib has demonstrated significant activity in patients with multiple myeloma and is a component drug in multiple myeloma treatment protocols.[2] It acts by inhibiting proteasomal degradation of intracellular proteins, accumulating intracellular misfolded proteins, resulting in cell cycle arrest, and subsequent induction of apoptosis in myeloma cells.[3] Although bortezomib has demonstrated significant improvement in patient outcomes, it is also associated with significant toxicities affecting the quality of life and adherence to treatment. Indeed, bortezomib can be potentially life-threatening.[4] Peripheral neuropathy is a dose-limiting toxicity linked to bortezomib, impacting as many as 34% of patients undergoing treatment for multiple myeloma.[5] The incidence of severe neuropathy resulting in foot drop is rare. Thus, we report this rare case of bortezomib-induced neuropathy resulting in foot drop in a patient with multiple myeloma on treatment and demonstrate the safe reintroduction of bortezomib.

CASE PRESENTATION

A man in his 50s presented to the oncology outpatient department with complaints of lower backache and oedema of both lower limbs for 3 months. He had type II diabetes with retinopathy, controlled with oral medication. Recently, he was diagnosed with chronic kidney disease due to diabetic nephropathy alongside hypertension. There is no personal history of tuberculosis, cardiovascular disease or malignancy. In his family, there was no reported similar illness or any genetic disease, including neuronal disease and malignancy. On clinical examination, he was found to be anaemic with bilateral pedal oedema. There was local tenderness over the lumbar vertebra while examining it, which elicited pain. His performance status scaled to European Cooperative Oncology Group score 1 with moderate build and nourishment. General systemic examination was within normal limits. The differential diagnosis consisted of lumbar radiculopathy, cerebrovascular accident and cerebellar ataxia.

After confirming the diagnosis of multiple myeloma, he was started on bortezomib-dexamethasone combination chemotherapy. He complained of pain and weakness in his right lower limb with difficulty in walking in the second week of chemotherapy. On examination, we found that he had a right-side foot drop (figure 1). There was no appreciable sensory loss in both legs. The power of the right leg remained except for a slight difficulty in dorsiflexion and getting off the floor while walking.

INVESTIGATIONS

Diagnostic evaluation of haematological parameters showed haemoglobin level, 78 g/L; total white blood cell (WBC) count, 5.4 × 10^9/L; differential counts with granulocytes, 65.7%; lymphocytes, 25.8%; monocytes, 8.5%; platelet count, 125 × 10^9/L; mean corpuscular volume, 80.0 fL; mean corpuscular haemoglobin, 31.0 pg; mean corpuscular haemoglobin concentration, 38.7 g/dL; haematocrit, 20.2%; red blood cell, 2.53 × 10^{12}/L; and red cell distribution width, 14.6%. His peripheral smear was normocytic normochromic, with few ovalocytes and elliptocytes with rouleaux formation; WBC counts within normal limits, neutrophils predomination and mild left shift; platelet count was just adequate, and platelets seen scattered singly, anisocytosis with large platelets suggestive of normocytic, normochromic anaemia. The biochemical parameters based on tests were blood urea, 25.5 mmol/L; serum creatinine, 653 µmol/L; serum albumin, 32 g/L; α-1 globulin, 3.5 g/L; α-2 globulin, 6.8 g/L; β-1 globulin, 1.7 g/L; β-2 globulin, 55.9 g/L; γ-globulin, 3.1 g/L; β-2 M spike, 50.5 g/L; and albumin globulin ratio, 0.45. An ultrasonogram of the abdomen showed that he had grade II renal parenchymal changes, an enlarged prostate, minimal ascites, mild splenomegaly and a small haemangioma of the right lobe of the liver.

Figure 1 Right side foot drop.

Immunotyping electrophoresis showed monoclonal bands in IgG and Igk. Serum immunoglobulins showed the following results: IgA, 3.51 g/L; IgG, 20.14 g/L; IgM, 2.14 g/L; serum free k (light chain), 26.22 mg/L; serum free l, 30.14 mg/L; and serum free k/l ratio of 0.86. Bone marrow aspiration cytology reported increased plasma cells (27%), seen in clusters and singly with immature and mature forms. Bone marrow trephine biopsy was reported as trilineage haematopoiesis admixed with haemorrhage and plasmacytosis (CD 138 positive) with k restriction. A skeletal survey of long bones and vertebrae showed a lytic region in the right humerus. The diagnosis is confirmed as multiple myeloma, and he was staged with International Staging System for multiple myeloma as stage II.

After medical neurology consultation, a nerve conduction study was performed, and it showed absent motor conduction in the right peroneal nerve and prolonged distal latency in bilateral median nerves. Compound muscle action potential was reduced in bilateral peroneal and median nerves. The conduction velocity was reduced in bilateral median nerves; F waves showed an absent response in bilateral peroneal nerves. Sensory conduction showed an absent response in bilateral superficial peroneal and bilateral median nerves. The final impression of the nerve conduction study was axonopathy in bilateral peroneal nerves and a demyelinating pattern in bilateral median nerves suggestive of bilateral carpal tunnel syndrome.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis consisted of lumbar radiculopathy, cerebrovascular accident and cerebellar ataxia. We ruled out lumbar radiculopathy because of the lack of typical symptoms, including pain, loss of sensation and associated tingling sensation. The patient also did not have any of the clinical symptoms associated with a cerebrovascular accident, including weakness down one side, sensation loss, difficulty speaking or understanding speech or personality changes. Except for the difficulty walking due to right-sided foot drop, there was no difficulty coordinating limb movements or unsteadiness to suggest cerebellar ataxia.

TREATMENT

Bortezomib was administered at a dose of 1.3 mg/m^2 intravenously every week and dexamethasone 40 mg orally weekly. After exhibiting foot drop, bortezomib was withheld, and he was continued on single-agent dexamethasone orally. Neuropathy was conservatively managed with analgesics and vitamin supplements.

OUTCOME AND FOLLOW-UP

Neuropathy gradually improved with time, and bortezomib was reintroduced successfully from the 15th week onwards without recurrence of foot drop. He later had a myeloma relapse and received multiple lines of chemotherapy, including the regimens that contain bortezomib and palliative radiation, still without the reappearance of foot drop (table 1).

DISCUSSION

Bortezomib is widely used to treat newly diagnosed and relapsed multiple myeloma and other haematological malignancies.[6] Over the years, bortezomib has demonstrated significant efficacy in improving treatment outcomes but has a few side effects. One

Table 1 Timeline of events

Background	Type II diabetes
Pre-existing	Chronic kidney disease Diabetic nephropathy Diabetic retinopathy
Year 0 (week 0)	Multiple myeloma BD regimen first cycle
Year 0 (week 1)	Lower limb weakness (foot drop) Bortezomib withdrawn
Year 0 (week 15)	Complete recovery of foot drop
Year 1	Bortezomib reintroduced (bortezomib + dexamethasone regimen)
Year 1	Palliative radiotherapy to right humerus Regimen: lenalidomide + dexamethasone + denosumab
Year 1	Rise in serum creatinine Stopped lenalidomide Started on pomalidomide
Year 1	Poor treatment tolerance Started bortezomib maintenance
Year 1	Disease worsening Started on cyclophosphamide + bortezomib + dexamethasone
Year 2	Continuing chemotherapy No residual neurological deficits

of the significant debilitating toxicities is bortezomib-induced peripheral neuropathy (BiPN), which affects the quality of life and compliance with treatment. Motor neuropathy manifests as foot drop, which is a rare and debilitating condition. The exact incidence of bortezomib-induced foot drop is unknown, possibly because of the rarity of this condition, the criteria to determine foot drop or the different multidrug regimens used for treating primary disease. It is crucial to identify this condition early to initiate corrective measures quickly.

Bortezomib-induced foot drop has an unknown aetiology. Although the exact mechanism of peripheral neuropathy associated with bortezomib is unclear, the molecular processes associated with peripheral neuropathy include mitochondrial damage, activation of T lymphocytes and monocytes, and increased sphingolipid metabolism, leading to neuronal inflammation and altered neuron excitability.[7] Direct neurotoxicity and microvascular damage may cause it. Bortezomib disrupts peripheral nerve proteasomes, causing axonal degradation and demyelination. Oxidative stress and inflammation can further damage nerves. Microvascular injury, including endothelial dysfunction and decreased blood flow, may potentially cause foot drop.[3] Further research is needed to determine the mechanisms of bortezomib-induced foot drop.

Peripheral neuropathy typically presents with sensory neuropathy in the extremities, including pain, numbness and tingling sensation, whereas motor neuropathy is characterised by muscle weakness.[8] The clinical manifestation of muscle weakness in the muscles responsible for dorsiflexion of the foot and toes characterises foot drop. Patients may report experiencing challenges in dorsiflexion, leading to a gait characterised by dragging or slapping of the foot. Typically, BiPN occurs during the first few weeks of treatment.[9] The degree of foot drop can vary, ranging from slight debility to total paralysis. Distinguishing bortezomib-induced foot drop from other peripheral neuropathy or musculoskeletal problems is crucial due to potential differences in therapeutic options.[10] Our patient also had a similar complaint, and he reported to the outpatient clinic that he had difficulty walking and a dragging foot early during treatment. Rarely, the neuropathy could be acute neurotoxicity syndrome, which differs from BiPN by not being a peripheral or distal involvement but leading to foot drop.[10] A case series study of six patients treated with bortezomib for multiple myeloma and light chain amyloidosis found that the age range at which foot drop occurs is 46–74 years.[10] Our patient also fell within this age range at the time of presentation with foot drop. Irrespective of the type of the light chain (k or l), such patients develop foot drop; our patient had k chain involvement. The route of administration of bortezomib could be another factor that influences the toxicity; however, foot drop is reported in patients receiving either subcutaneous or intravenous preparation; our patient received an intravenous preparation.[10] Even though the occurrence of foot drop is commonly seen in the first few weeks of bortezomib introduction, it could even occur after stopping the drug. Our patient developed foot drop with one cycle, similar to the reported series where two patients developed foot drop following the first cycle of bortezomib.[10] The predisposing factors for BiPN include an increased cumulative dose of the drug, pre-existing peripheral neuropathies, paraproteinemia, diabetes mellitus, alcohol abuse, intravenous use, coadministration of thalidomide, vitamin deficiency and viral infections that can aggravate peripheral neuropathy.[11 12] It is important to consider here that our patient had pre-existing type II diabetes and diabetic nephropathy, which could have initiated the neuropathy.

The primary approach to managing bortezomib-induced foot drop is to focus on providing support measures and making adjustments to the dosage of the drug. Physiotherapy is essential for enhancing muscle strength and correcting irregular walking patterns. It may be required to employ analgesics or neuropathic pain drugs for pain management. If the symptoms become intolerable, it may be necessary to temporarily or permanently reduce the dosage of bortezomib or discontinue its use.[13] Our patient had improved with the temporary discontinuation of the drug along with supportive measures. Bortezomib-based regimens can be reintroduced in patients; the incidence and pattern of toxicities reveal that bortezomib can be used without additional toxicities.[14 15] However, reintroduction is challenging, as seen in the reported case series, where one patient who recovered from a foot drop following bortezomib recurred after rechallenging with it.[10] Fortunately, we could restart our patient on bortezomib after a few weeks without a recurrence of foot drop.

There is no established preventive treatment for BiPN, even though several approaches have been attempted, including dose modifications and nutraceutical compounds, including L-arginine, nervonic acid, Curcuma rhizome and acetyl-L-carnitine.[16 17] The use of analgesics is also controversial; as such, only modest pain relief is obtained with the use of combinations of analgesics because of the severity of the neuronal damage that occurs.[18] We used analgesics and multivitamin supplements in our patient; however, we could not quantify the benefit, even though he had symptomatic improvement after a few weeks.

The challenges we faced were identifying BiPN early during treatment to prevent the progression of foot drop and further complications associated with it. Distinguishing BiPN from other causes of peripheral neuropathy and pre-existing disease, especially with associated diabetes mellitus, was challenging in treating this patient. We had to balance the treatment for multiple myeloma with the continuation of steroids alone with the temporary discontinuation of bortezomib. Because of the lack of preventive strategies, we had to rely on trial-and-error methods for the safe reintroduction of bortezomib and close monitoring of neuropathic symptoms. Although foot drop is rare with bortezomib use, we could identify the condition early in the course and evaluate it clinically. Instead of permanently discontinuing bortezomib, we made it a part of treatment, being an active drug, and could safely re-administer it at the earliest opportunity. Our findings, being based on a single patient, have limited generalisability to a broader population. Long-term follow-up will be required to assess the sustainability of neuropathy resolution.

In conclusion, bortezomib-induced foot drop is a rare but potentially debilitating complication of bortezomib-based therapy in multiple myeloma. Understanding the pathophysiology, clinical presentation, management and potential preventive strategies is crucial to everyone caring for patients with myeloma. Early recognition of neuropathy, prompt intervention and multidisciplinary management can help minimise the impact of foot drop on quality of life. There is a need for further research to understand better the underlying mechanisms for effective prevention and treatment of peripheral neuropathy induced by bortezomib.

Patient's perspective

I noticed something was not right as I had started to having pain in my back for quite a while. As days passed, it became more bothersome, and I started having swelling in both legs. This was concerning to me as I was already managing my diabetes, and I knew the importance of changes happening to my body. I sought medical attention to find out the cause of this trouble; the doctors I consulted were quite helpful in relieving my concerns. They examined me and ran a few blood tests and X-ray examination which gave the suspicion of a disease affecting my marrow. They checked my marrow and confirmed that I have a disease called multiple myeloma and suggested that I take treatment. I agreed to take a few courses of injections called chemotherapy. Starting treatment seemed like the right step forward, but it was not long before I encountered a new challenge. I found myself unable to walk and lift my foot correctly while walking, leading to what doctors called a 'foot drop'. When walking became a difficult task, once again, I became very anxious, but doctors reassured me. With the advice of doctors, I had to adjust my treatment and drop a few medications, which caused this trouble. Gradually, I could walk again. The battle was tough, but I could manage it well with the care and support I got. I had a few ups and downs during my struggle with this disease, but I continue to fight, and I am hopeful that with the right kind of treatment, I can overcome all the challenges that come my way.

Learning points

- Bortezomib-induced peripheral neuropathy (BiPN) is a significant side effect of bortezomib-based treatment in multiple myeloma, and a high index of suspicion is required in patients presenting with weakness of extremities.
- The inability to dorsiflex the foot is characteristic of foot drop and BiPN and should be confirmed by nerve conduction studies, which show absent nerve conduction.
- Pre-existing diabetes mellitus and other comorbidities predispose to BiPN, and clinicians should closely monitor for BiPN in patients.
- Bortezomib must be temporarily discontinued in patients with BiPN; reintroduction may be considered if the benefits outweigh the risks.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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