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Case Report

# Ibrutinib induced sensorimotor neuropathy: A novel side effect

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a well-documented toxicity leading to dose limitation.
Ibrutinib is an oral Bruton's Tyrosine Kinase (BTK) inhibitor approved for treating chronic lymphocytic lymphoma. The most common neurological side effects of Ibrutinib include headache and dizziness. Herein, we report peripheral neuropathy as a dose-limiting manifestation of Ibrutinib treatment.



## 1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a well-documented toxicity leading to dose limitation. The most common symptoms mentioned in literature are pain and paresthesia, which are partially reversible.[1] CIPN development may often lead to dose reduction or change in the chemotherapeutic agent from the treatment protocol.[2]

Ibrutinib is an oral Bruton's Tyrosine Kinase (BTK) inhibitor approved for treating chronic lymphocytic lymphoma. Ibrutinib's neurological side effect profile includes headache and dizziness in > 10% of recipients.[3] Herein, we report peripheral neuropathy as a dose-limiting manifestation of Ibrutinib treatment.

## 2. Case Report

A gentleman in his seventh decade, with no prior comorbidities, visited our outpatient department two years back with complaints of weight loss of around 8 kilograms over five months and painless progressive lymphadenopathy on both sides of the neck for three months. His medical history was negative for fever or drenching night sweats. He was thoroughly investigated, and his complete blood count revealed leucocytosis with lymphocytosis. His initial haemoglobin level was 11.1 gm/dl, total leucocyte count was 2,24,600/mm3 with a lymphocyte count of 2,09,000/mm3, and platelet count was 1,29,000/mm3. Both direct and indirect Coomb's tests were negative. His immunoglobulin levels were evaluated, and all three (IgG, IgA, IgM) were within normal limits. Peripheral smear examination showed four smudge cells. On further evaluation, flow cytometry suggested bright positivity for CD19, CD20, and CD200 and moderate for CD5, and CD23. His ZAP 70 was negative (3.1%), and mutation analysis for 17p deletion was negative. Whole body PET-CT evaluation was done, which revealed bilateral cervical lymphadenopathy in all levels, most significant in the left posterior cervical region (2.1x1.2 cm, SUV max 8.32), bilateral supraclavicular lymph nodes, bilateral axillary lymph nodes (largest in the left axilla, 2.4x1.3 cm, SUV max 6.28) conglomerate abdominal lymph nodes (2.2x1.6 cm, SUV max 5.43), diffuse fatty infiltration of liver and splenomegaly (14.9 cm). His viral markers were negative. The size of his neck nodes increased while he was being evaluated. He was then diagnosed with chronic lymphocytic

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leukaemia (CLL), RAI stage II. He was started on Tab. Ibrutinib 420 mg once daily abd was routinely followed up with blood investigations and clinical examination. On a follow-up visit, after 28 months of taking Tab. Ibrutinib, he complained of difficulty in walking and decreased sensation in both feet. On examination, Romberg test was negative, bilateral ankle reflexes were weak, a light touch sensation was absent over the left sole and lateral aspect of the leg, pain and temperature sensations were intact, and joint position sense was present. An evaluation to rule out metabolic causes of paraesthesia was carried out. However, his blood sugar level, including HbA1c, was within normal limits; vitamin D level was in the normal range, serum folate level was 3.9 ng/ml, and serum vitamin B12 level was 234 pg/ml. He did not give a positive history of alcohol intake or smoking. A PET-CT scan was done for disease assessment, and the patient was in complete remission.

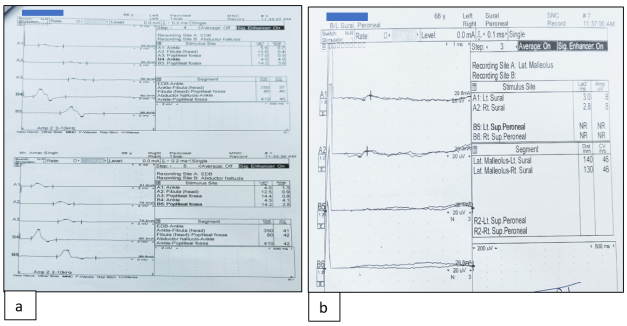


**Fig. 1: a & b:** Nerve conduction velocity test

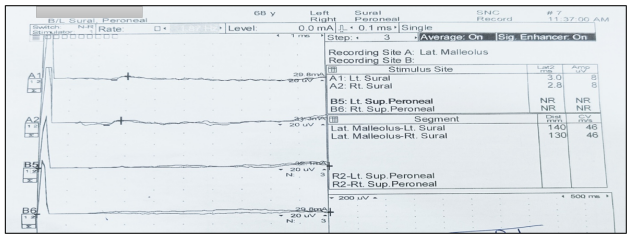

**Fig. 2:** Nerve conduction velocity test of sural and peroneal nerve

Nerve conduction studies were carried out for bilateral lower limbs and revealed low amplitude CMAPs (compound muscle action potential) in foot muscles, 90.7 mv in extensor digitorum brevis (EDB), and four mv in Abductor hallucis (AHB) with average motor nerve conduction velocity (NCV) in Peroneal and Tibial nerves. Tibial F waves were at 61-63 ms. The Tibial H reflex was absent on the left and weakly elicited on the right. Sensory potentials in Superficial peroneal nerves were absent, and low amplitude 8mv in Sural nerves. Overall findings revealed length-dependent sensory-motor neuropathy (Figure 1). Given the progression of symptoms, he was advised to discontinue Tab Ibrutinib with a follow-up after one month. On his follow-up visit, symptoms were improved, and hence based on the history and clinical evaluation, a diagnosis of Ibrutinib-induced neuropathy was established. Currently, the patient is on observation as his disease is in remission.

## 3. Discussion

Chemotherapeutics agents act upon peripheral nervous system (PNS) structures to produce neuronopathy, axonopathy or myelinopathy responsible for CIPN.[4] The usual presentation of CIPN is a "glove and stocking" pattern, mainly in the feet and hands, as long nerves are more susceptible to CIPN. Patients may experience various symptoms, including paraesthesia, dysesthesia, allodynia, hyperalgesia, hypoalgesia or pain that is burning, shooting or electric-shock-like sensation.[5] Apart from chemotherapeutic agents, other etiological factors for CIPN include age, comorbid conditions like diabetes that can potentially cause nerve damage and the use of alcohol.[6] Ibrutinib is the BTK inhibitor approved for treating chronic lymphocytic leukaemia (CLL)/small lymphocytic leukaemia (SLL). It has oral bioavailability and binds irreversibly to BTK.[7] The recommended dosage of Oral Tab. ibrutinib for CLL is 420 mg until disease progression or intolerance by the patient.[8] Some common toxicities documented for discontinuation of treatment included arthralgias, atrial fibrillation, cytopenia, pneumonitis, bleeding and diarrhoea.[8] In a retrospective series of CLL patients (n = 616) treated with Tab. ibrutinib, the discontinuation rate was 41% due to toxicity rather than disease progression.[9] After an extensive literature search, only two cases were reported to have ibrutinib-induced neuropathy. Supernova A.N. et al.[10] reported ibrutinib-induced peripheral neuropathy after five months of therapy, and Comert et al.[11] reported a similar side effect profile of neuropathy after ten months of Ibrutinib treatment.

## 4. Conclusion

The case being reported is a male in his seventh decade with no prior comorbidities, diagnosed with CLL experiencing a unique side effect of Tab. Ibrutinib that is neuropathy. To the best of our knowledge, till now only two cases have been reported with this novel side effect. It is being presented to clinicians that one should be aware of all the potential side effects of the drug. Awareness regarding novel side effects is vital to avoid misdiagnosis and complications.

## 5. Source of Funding

None.

## 6. Conflict of Interest

None.

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