

Severe Vincristine-Induced Peripheral Neuropathic Weakness in Both Lower Limbs in an Asian Adolescent with *CYP3A4* rs2740574 TT Genotype

Dongdong Zhang ¹, Jie Bai²

¹Department of Oncology, Xiangyang No. 1 People's Hospital, Hubei University of Medicine, Xiangyang, 441000, People's Republic of China;

²Department of Neurology, Xiangyang No. 1 People's Hospital, Hubei University of Medicine, Xiangyang, People's Republic of China

Correspondence: Dongdong Zhang, Department of Oncology, Xiangyang No. 1 People's Hospital, Hubei University of Medicine, Jiefang Road No. 15, Xiangyang, Hubei, 441000, People's Republic of China, Tel +8615072278600, Email zhangdongdong@whu.edu.cn

Background: Vincristine (VCR)-induced peripheral neuropathy (VIPN) is a common adverse reaction during cancer treatment, typically characterized by numbness and paresthesias. This study aimed to report a rare case of VIPN with an atypical genotype, manifesting as grade 3 weakness of the lower limbs.

Case Presentation: A 19-year-old man, diagnosed with alveolar rhabdomyosarcoma for 8 months, was transferred to our hospital for further treatment after the failure of first-line treatment. He developed severe long-standing weakness in both lower limbs and could not walk after four sessions of second-line chemotherapy. The diagnosis of VIPN was confirmed based on the patient's physical examination, imaging studies, electromyogram results, and treatment history. Furthermore, the pharmacogenetic analysis indicated that the patient harbored *CYP3A4* rs2740574 TT genotypes.

Conclusion: We have reported for the first time a VIPN patient whose main clinical manifestation is severe weakness in both lower limbs, accompanied by the *CYP3A4* rs2740574 TT phenotype. This case may provide new information on the phenotypic features of VIPN, and may help to better understand the disease pathogenesis and contributing factors.

Keywords: vincristine, vincristine-induced peripheral neuropathy, *CYP3A4* rs2740574 TT genotype

Introduction

Vinca alkaloids (VAs) are the earliest and classic microtubule-targeting agents that can interfere with continuous mitotic division and disrupt cancer cell growth.¹ VCR is one of the most important VAs incorporated into several polychemotherapy regimens for the treatment of hematological malignancies, lymphoma, sarcomas and pediatric cancers. However, the dose-limiting side effects caused by VCR can potentially lead to treatment discontinuations and interruptions, and even impact the patients' quality of life.

VIPN is the most common adverse reaction in clinical practice. As VCR can poorly penetrate across the blood-brain barrier, the occurrence of central nervous system toxicity is relatively low. The VIPN etiology is mainly associated with the disruption of microtubule structures, axonal dysfunction, and inflammation.² VIPN can be categorized into sensory neuropathy, autonomic neuropathy, and motor neuropathy based on clinical symptoms.² Sensory neuropathy is more common, with paresthesia, numbness, neuropathic pain or jaw pain, and sensory abnormalities as the main clinical manifestations. Autonomic neuropathy can manifest as symptoms such as urinary retention, constipation, and so on.³ However, manifestations of autonomic neurotoxicity are difficult to identify because symptoms are easily confused with other treatment-related side effects. Motor neuropathy can be presented as extremity weakness, walking difficulties, and impaired balance, and its incidence is relatively high in pediatric patients with cancer receiving long-time VCR-based treatment. Further, these symptoms usually develop early during treatment and persist for a relatively long time.⁴

Currently, the Common Terminology Criteria for Adverse Events and Total Neuropathy Score-Pediatric Vincristine tools are commonly used for evaluating VIPN.^{5,6} Previous studies have shown that multiple factors contribute to the

development and severity of VIPN, including age, genetic ancestry, dose, impaired liver function, combination medicine and single-nucleotide polymorphisms (SNPs).⁷⁻⁹ Previous studies indicated that *CYP3A4* was not prevalent in Asian. However, *CYP3A4* rs2740574 genotype commonly associated with a severe peripheral neurotoxicity associated with taxanes.¹⁰ This study reported a rare case of VIPN presenting as severe weakness in both lower limbs in an Asian adolescent harboring an uncommon *CYP3A4* rs2740574 TT genotype.

Case Presentation

A 19-year-old obese male, complaining of protruding eyeballs, accompanied with decreased and blurred vision for 1 day, was admitted to Guangzhou People's Hospital. Magnetic resonance imaging (MRI) suggested a mass in the left ethmoid sinus and orbit, with compressed left medial rectus muscle, leading to the eyeball protrusion. He then underwent endoscopic excision of the nasal mass. Postoperative pathology indicated alveolar rhabdomyosarcoma (RMS) of the left ethmoid sinus (Intergroup Rhabdomyosarcoma Study group III, an intermediate risk group). The patient then received postoperative adjuvant chemotherapy according to the Chinese Children Cancer Group Rhabdomyosarcoma 2016 regimen.¹¹ Unfortunately, he experienced persistent headaches for 10 days after the completion of the 10th chemotherapy session. The patient visited our hospital seeking further examination and treatment. MRI indicated a hyperintense lesion on the T1- and T2-weighted image on the lateral wall of the orbit, extensive meningeal metastasis, multiple intracranial metastases, and bilateral multiple cervical lymphadenopathy, suggesting tumor recurrence and progression (Figure S1). The patient received concurrent chemoradiotherapy, and intrathecal chemotherapy drugs were administered before each chemotherapy session simultaneously. The patient's symptoms relieved after the completion of the first session of chemotherapy. The brain metastases significantly reduced in size after the completion of four sessions of chemotherapy (Figure 1); however, the patient experienced weakness in both lower limbs and walking difficulty, the weakness spreads gradually from the distal end to the proximal end within 5 days. The physical examination suggested normal muscle strength in both upper limbs, but the muscle strength in both lower limbs was graded as 3 in the proximal muscles. The pathological reflex was negative. The cranial MRI, vertebral MRI, and cerebrospinal fluid analysis did not reveal any significant abnormality. The electromyogram (EMG) revealed a reduction in the motor conduction velocity, and the evoked potentials indicated prolonged latency of peripheral nerve action potentials, suggesting peripheral neuropathy (Figure 2).

The patient received a cumulative dose of 28 mg of VCR during both first-line and second-line treatments, we confirmed the diagnosis of VIPN based on the patient's long-term history of VCR treatment and the results of EMG. Furthermore, we performed a gene polymorphism analysis to investigate potential factors that could influence the occurrence of VIPN. The pharmacogenetic results revealed the presence of a complex pattern of polymorphisms, including the following genotypes: *CYP3A4* rs2740574 TT and *CEP72* rs924607 CC genotypes (Figure 3). The patient's symptoms relieved gradually after oral administration of pyridoxine (vitamin B6), glutamine, and pyridostigmine.

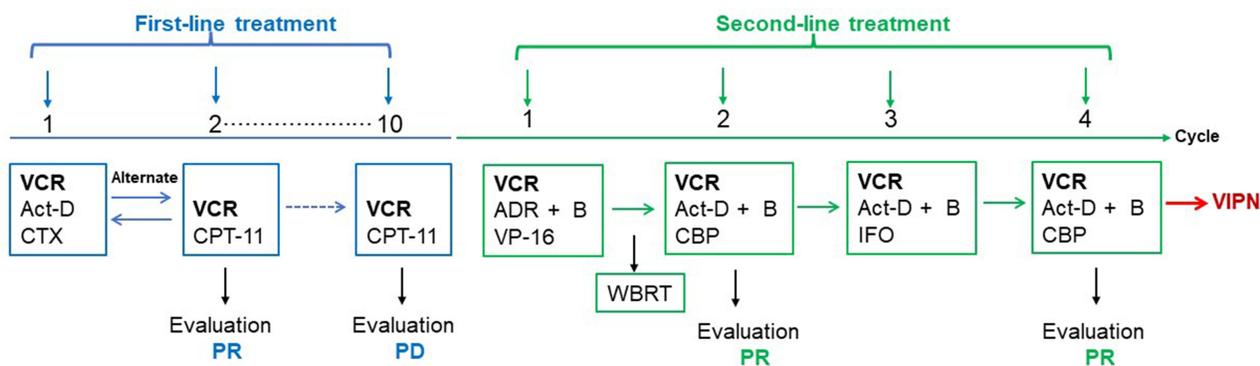


Figure 1 The treatment flow chart. VCR, vincristine, 1.5 mg/m² (Dmax= 2.0 mg), d1, d8, d15; Act-D, actinomycin D, 0.045 mg/kg (Dmax=2.5 mg), d1; CTX, cyclophosphamide, 1.2 g/m², d1; CPT-11, irinotecan, 50 mg/m², d1-d5; ADR, Adriamycin, 30 mg/m², d1-d2; VP-16, etoposide, 150 mg/m², d1-d3; B, bevacizumab, 7.5 mg/kg, d1; CBP, carboplatin, 560 mg/m², d1; IFO, ifosfamide, 1.8 g/m², d1-d5; all chemotherapy regimens are repeated every 21 days. PR, partial remission; PD, disease progression.

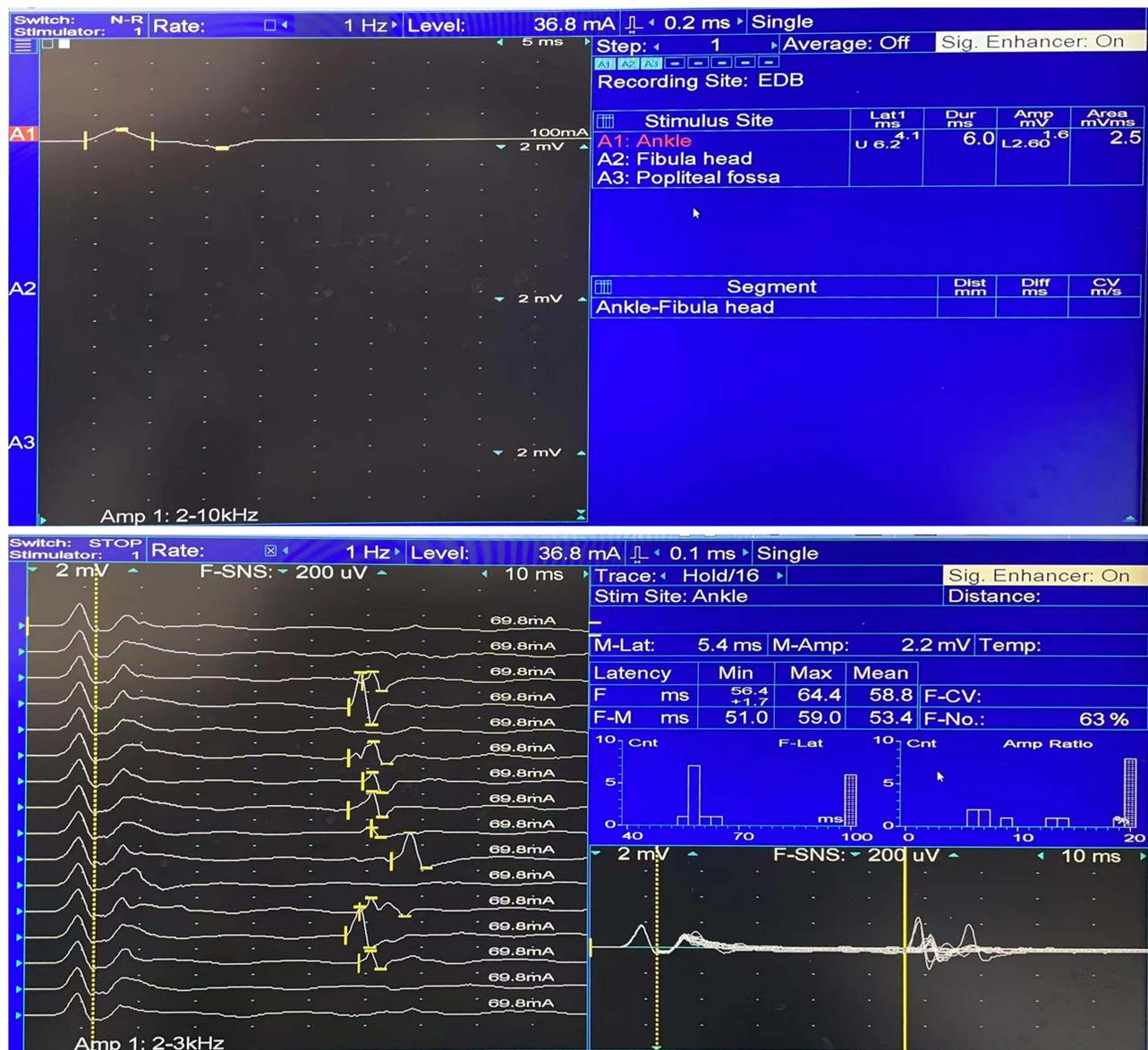


Figure 2 EMG indicated reduced motor conduction velocity and prolonged latency of F-wave.

Discussion

Since the introduction of VCR as a chemotherapeutic agent for treating cancer in 1962, its most significant neurotoxic side effect, especially symmetric sensory-motor neuropathy, has been widely studied and closely monitored in clinical settings.¹² This study reported an adolescent with refractory rhabdomyosarcoma developing dose-limiting VIPN whose complex and atypical pattern of genetic polymorphisms might be the cause of severe extremity weakness.

Multiple factors are involved in the development and severity of VIPN, and they are often interrelated. VIPN is a dose-limiting side effect, and one of these factors is the dose of administration, including the cumulative dose and maximum single dose. When the cumulative dose of VCR exceeds 2–6 mg/m², approximately 35–45% of patients are at risk of developing VIPN.¹³ Previous studies have shown that higher single doses of VCR are associated with an increased occurrence and severity of VIPN.¹⁴ This validated the recommended VCR dose administration: 0.05–0.065 mg/kg in infants and 1.3 mg/m² in children and adults, with a maximum single dose of 2 mg.⁸ The next factor was the administration frequency of VCR. Rosca et al discovered that when the administration of VCR was more closely spaced, the incidence of VIPN also increased accordingly.¹⁵ This finding suggested that VCR should be administered with a minimum of 1-week

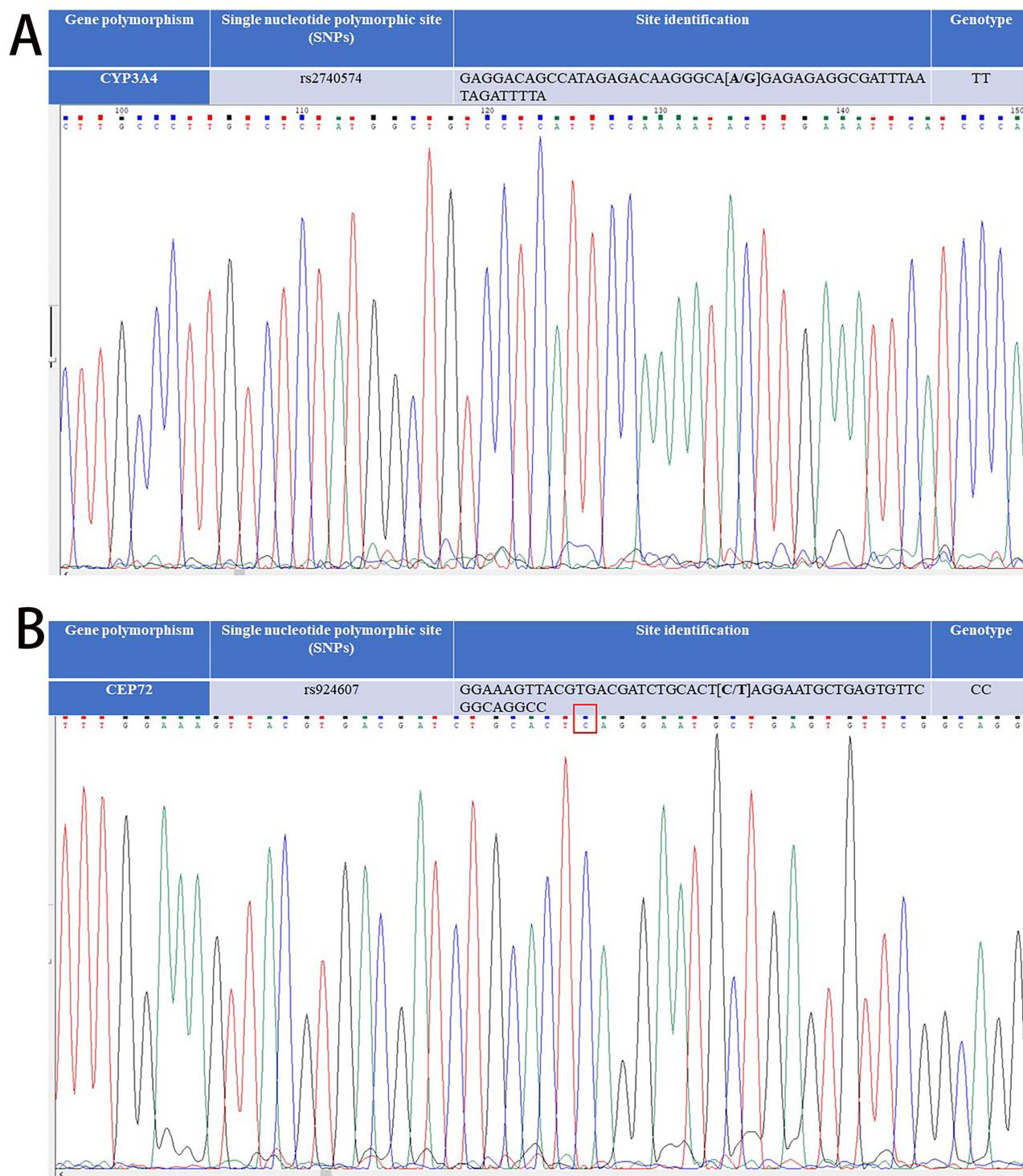


Figure 3 Sanger sequencing indicates the presence of both *CYP3A4* rs2740574 TT (**A**) and *CEP72* rs924607 CC genotypes (**B**).

interval between each dose. Furthermore, the method of administration is also related to the risk of developing VIPN. The standard route of administration for VCR is bolus push injection, and continuous infusion seems to increase systemic exposure.¹⁶ Prolonged infusion can increase the systemic exposure of VCR. One systemic review showed that VCR bolus injections over 1–5 min, which may increase inter-compartmental clearance and high peak-plasma concentrations, induced a higher incidence of VIPN compared with prolonged 1-h infusion.⁸ However, a randomized study indicated no significant

difference in the incidence of VIPN between the 1-h infusion group and the VCR push injection group.¹⁷ Notably, VCR was metabolized in the liver through the CYP3A4 enzymes. CYP3A4 inhibitors, such as azole antifungals, could slow down the clearance of VCR, thereby increasing the risk of developing VIPN.¹⁸ However, 1-h infusions were advantageous in reducing the risk of VIPN, especially in patients who received concurrent azole therapy.¹⁷

Patient-related factors influence the risk of developing VIPN. Although a significant inter-individual variability in VCR pharmacokinetics has been observed, previous studies have indicated that children have a higher plasma clearance than adults; this diminished drug exposure may lower the risk of developing VIPN.¹⁶ Certain genetic variations can affect the metabolism and clearance of VCR, thereby impacting the risk of developing VIPN. The aforementioned CYP3A enzyme, including CYP3A4 and CYP3A5, is primarily responsible for drug metabolism. CYP3A4 and CYP3A5 genes are present in all ethnicities, while CYP3A4 is prevalent in Caucasians, the Chinese population accounts for only 30% of the total population,¹⁹ CYP3A5 is commonly found in 45% of Africans-Americans, only 7% of East Asian.²⁰ CYP3A5 has been identified as a more selective and efficient metabolizer of VCR than CYP3A4.²¹ Individuals with the *CYP3A5**3/*3 genotype are typically considered to have very low or no expression of the CYP3A5. These patients have a lower predicted VCR clearance rate compared to individuals who express CYP3A5. Some studies indicated that expression of the *CYP3A5**3/*3 genotype was typically associated with an increased risk of VIPN.²⁰ However, some other studies and a recent meta-analysis demonstrated that CYP3A5 expression status had no significant impact on the development of VIPN.^{22–24} Studies have identified that patients with the *CYP3A4* loss-of-function variants and missense variants have a higher risk of neurotoxicity.²⁵ In this study, the Asian adolescent developed severe neurotoxicity, which may be associated with the *CYP3A4* TT genotype. Due to limited testing panel and the patient's poor economic condition, we did not perform a single test for CYP3A5 polymorphism.

CEP72 promoter polymorphism is closely associated with the occurrence of VIPN.²⁶ Further, studies have demonstrated that the *CEP72* rs924607 TT genotype induces a higher rate of severe VIPN than the CC or CT genotypes.²⁷ However, some other studies have indicated no association between the early occurrence of VIPN and the *CEP72* rs924607 TT genotype.²⁸ Gutierrez et al found that patients with the *CEP72* CT genotype had a higher risk and severity of VIPN occurrence compared with those with the TT or CC genotype in a Spanish population; and patients with *CEP72* CC genotype had the lowest risk of developing grade 2–4 neurotoxicity in their results.²⁸ Although rare, we presented a case with the *CEP72* CC genotype developing severe VIPN in an Asian individual.

Other reported genes related to VIPN, such as *ABCC1* and *ABCB1*, *SLC5A7* and *TTPA*, do not directly contribute to the occurrence of VIPN. Nevertheless, the polymorphisms of these genes may be related to the susceptibility of VIPN.^{29,30} Therefore, there are no highly selective and widely accepted biomarkers available for predicting the occurrence of VIPN. However, our study indicated that SNP testing was of certain significance in predicting VIPN.

Obesity is one of the nongenetic factors correlated with VIPN.³¹ This can be explained by the release of pro-inflammatory cytokines and the storage of VCR in adipose tissue, which may enhance the neurotoxicity of VCR. Besides previously mentioned azole antifungals, some antiemetic drugs, such as aprepitant and fosaprepitant, can also lead to the occurrence of VIPN as they have moderate inhibition on CYP3A4.³² The patient in our study is moderately obese and has a history of using fluconazole and aripiprazole, both of which may be factors contributing to the occurrence of VIPN. Thus, the choice of antiemetic drugs should take into consideration the risk of developing VIPN during VCR-containing regimens treatment.

Currently, no unified standard exists for preventing and treating VIPN. It is recommended to avoid long-term and repetitive use of VCR. When VIPN occurs, the dosage of VCR should be reduced or discontinued depending on the patient's condition. Pyridoxine has neuroprotective effects and can be used for treating VIPN. Pyridoxine plus pyridostigmine therapy has been confirmed to be an effective treatment for VIPN.³³ The recommended doses for pyridoxine and pyridostigmine are 150 mg/(m²·day) and 3 mg/(kg·day), respectively. Glutamate, as an excitatory neurotransmitter, also possesses some neuroprotective properties. Glutamine supplements can enhance sensory function and overall quality of life, with a recommended dose of 6 g/m² administered twice daily for 21 days.³⁴ Gabapentin can be used to treat neuropathic pain at an initial dosage of 5–10 mg/(kg·day) [with a maximum of 50–70 mg/(kg·day)]. Opioid drugs can be introduced if the pain control is not satisfactory. Additionally, capsaicin can also be used for topical treatment of peripheral neuropathic pain.³⁵

The limitation of this study is that we did not conduct whole exome sequencing, so we cannot definitively determine the status of all other genes related to peripheral neuropathy. Additionally, this study is a case report, and we can only speculate that VIPN may be related to *CYP3A4*. Further large-scale clinical trials are still needed to validate this hypothesis.

In conclusion, we presented a case of VIPN in a patient presenting mainly with severe bilateral lower-limb weakness harboring *CYP3A4* rs2740574 TT genotypes. We also reviewed the risk factors and treatment strategies for VIPN. Currently, no widely accepted genetic biomarkers have been reported for predicting VIPN. Further studies are needed to develop a comprehensive risk assessment system to better understand the safe and individualized use of VCR in patients.

Data Sharing Statement

The clinical data supporting the conclusions of this manuscript will be made available by the corresponding author.

Ethics Approval

This study was approved by the Ethics and Scientific Committee of Hubei University of Medicine with approval number 2022PR-H002. Written informed consent was obtained from the individual for the publication of any potentially identifiable images included in this article. Institutional approval was also obtained to publish the case details.

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Disclosure

The authors declare that they have no competing interests in this work.

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