IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 9 Ser. 6 (September. 2024), PP 45-47
www.iosrjournals.org

"Voriconazole-Associated Motor Neuropathy In Acute Myeloid Leukemia: A Case Report And Literature Review"

Neha Sivani Rajavasireddy
Siddhartha Medical College

Sai Nitish Rajavasireddy
Siddhartha Medical College

Anil Aribandi
Consultant Hematologist, American Oncology Institute

Ranjith Kumar CS
Consultant Hematologist, American Oncology Institute

Abstract:
Introduction: Voriconazole, a commonly used antifungal in immunocompromised patients is effective against various fungal pathogens.
Despite its efficacy, it is associated with numerous adverse effects, including the less frequently documented motor neuropathy.
Case Presentation: We report a case of a 60-year-old male with acute myeloid leukemia (AML) who developed motor neuropathy following voriconazole administration. Initially treated with standard chemotherapy and prophylactic antifungals, he developed febrile neutropenia and was subsequently administered voriconazole. Within a week, he presented with bilateral foot drop.
The neurological assessment revealed severe motor weakness without sensory loss. MRI indicated lumbar disc protrusion and nerve conduction studies confirmed severe demyelinating polyneuropathy. Upon cessation of voriconazole, the patient's symptoms completely resolved, as confirmed by follow-up electromyography.
Discussion: Voriconazole-associated neuropathy, though rare, can present as motor neuropathy, contrary to the more commonly reported sensory neuropathy.
The exact mechanism remains unclear, and while symptoms often resolve after discontinuation, some cases may result in permanent damage.
Conclusion: This case highlights the importance of recognizing voriconazole-induced motor neuropathy in AML patients. Early identification and discontinuation of the drug are crucial for symptom resolution. Further research is needed to understand the underlying mechanisms and to develop preventive and management strategies.

Keywords: *Antifungal agents Voriconazole, Electromyography, nerve conduction studies, motor neuropathy*

Date of Submission: 09-09-2024 Date of Acceptance: 19-09-2024

I. Introduction:

"Fungal infections are common among immunosuppressed cancer patients, particularly those with hematological malignancies (1). Antifungal drugs are advised during the treatment course, either as prophylaxis or for probable or proven fungal infections. Prolonged therapy is often required, and among antifungals, azoles are commonly used. Voriconazole is a well-recommended drug for both prophylaxis and treatment purposes, as recommended by many clinical guidelines (2).

Its effectiveness against a broad spectrum of fungal pathogens, including Aspergillus species, Candida species, and others make it a valuable therapeutic option. Clinical guidelines often recommend voriconazole due to its efficacy and relatively low incidence of resistance compared to other antifungal agents.

However, voriconazole does cause many adverse effects; neuropathy is less documented (3). Common adverse effects of voriconazole include visual disturbances, hepatotoxicity, gastrointestinal disturbances, and

skin reactions. Here, we report a case of voriconazole-associated motor neuropathy in acute myeloid leukemia and review the literature on various types of voriconazole-associated neuropathy."

II. Case Presentation:

A 60-year-old gentleman was diagnosed with Acute Myeloid Leukemia (AML) M4/M5 with a background of Myelodysplastic Syndrome (MDS) in October 2017. He did not mention any previous comorbidities such as diabetes mellitus, hypertension, or coronary artery disease. He was given standard 3+7 induction chemotherapy with Daunorubicin intravenous bolus (60 mg/m2/day x 3 days) and Cytarabine infusion (100 mg/m2/day x 7 days). Concurrently, he was administered Posaconazole at 200 mg three times a day orally and acyclovir 400 mg twice a day for prophylaxis.

On day 11 of induction, he developed febrile neutropenia for which he received standard antibiotics (Inj. Meropenem and Inj. Colistin). Due to a spiking fever on day 15 of induction, Voriconazole was initiated at a loading dose of 6 mg/kg followed by 4 mg/kg twice daily. On day 21, he developed bilateral foot drop. A neurologist's opinion was sought, and on examination, he was found to have motor weakness with bilateral foot drop and power in the lower limb of 1/5, with normal sensory, bowel, and bladder examination. The cranial nerve and higher functions were normal. Magnetic Resonance Imaging (MRI) of the lumbar spine and nerve conduction studies (NCS) were performed for further evaluation. MRI suggested disc protrusion at the L3-L5 level with mild thecal compression. NCS revealed severe demyelinating polyneuropathy with a significant reduction of the posterior tibial and peroneal nerve conduction velocities. Needle electromyography showed mild denervation of the right anterior tibialis muscle and theorbicularis oris. The peroneal and posterior tibial nerve compound muscle action potentials were of low amplitude, with values of 0.2 and 0.5 mV, respectively (normal range, 3-30 mV), along with marginally prolonged distal latencies for the same nerves. Motor conduction velocities and F-wave study findings were also consistent with demyelination. Slowed motor conduction velocities were observed bilaterally for the peroneal (36 m/s [lower normal value, 45 m/s]) and the right posterior tibial (27 m/s [lower normal value, 42 m/s]) nerves. The F-wave value was 65 milliseconds for the right posterior tibial nerve and 62 milliseconds for the left peroneal nerve. Sensory conduction velocities of the sural nerves bilaterally were normal. An electromyographic evaluation revealed a few fibrillation potentials and a reduced (interference pattern) maximal contraction diagram in the tibialis anterior muscle.

Upon stopping Voriconazole, he experienced complete recovery. All plausible causes were considered and evaluated, and his serum electrolytes were normal. A follow-up electromyogram revealed complete reversal of the earlier neuropathy and was normal.

III. Discussion And Literature Review:

Voriconazole, an antifungal agent in clinical use for over a decade, demonstrates good activity against several Candida species, Aspergillus species, and other filamentous fungi (4). Metabolized in the liver, dose adjustment is necessary for patients with hepatic impairment. We present a case of voriconazole-associated peripheral neuropathy.

Peripheral neuropathy, a significant adverse effect of several medications, has been linked to antifungal drugs such as azoles and the amphotericin group (5).

Voriconazole-induced neuropathy is documented as a less common (<2%) adverse effect, more prevalent in patients with comorbidities like diabetes, hypothyroidism, renal or hepatic dysfunction, and concomitant medication use, particularly in cancer patients alongside Vinca alkaloids (6).

Our patient developed motor neuropathy following voriconazole administration, contrary to the literature where painful sensory neuropathy is more common, occurring in about 10% of long-term users. However, with itraconazole and posaconazole, neuropathy was documented in about 17% and 3% respectively (7). While most neuropathies associated with azole therapy are predominantly sensory, bilateral lower limb motor weakness and quadriparesis have been documented (7). Most cases resolve upon therapy cessation, though some individuals experience irreversible damage despite discontinuation (8).

The mechanism of voriconazole/triazole-induced neuropathy, like other toxic neuropathies, remains unclear. Although theoretically serum concentration-dependent, a retrospective study found all cases of voriconazole-induced neuropathy occurred with drug levels below the maximum target therapeutic level (7). Thus, prevention and identification of susceptible individuals are crucial.

Symptoms typically develop over 1-4 weeks, with a median onset of 3 months. Most patients experience symptom resolution within 1 month of cessation, but there's no evidence yet on which patients may have persistent deficits. Unlike chemotherapy-induced and diabetic neuropathy, there are no grading systems for triazole-induced neuropathy, underscoring the importance of prevention and early diagnosis (9).

Treatment for voriconazole-induced neuropathy is not well-documented. Cessation of therapy resolves most symptoms, though relief may be found with cold application, intravenous methylprednisolone, and magnesium infusion (10).

IV. Conclusion:

We presented a case of voriconazole-associated motor neuropathy in a patient with acute myeloid leukemia, a rare but noteworthy complication. Unlike the more common sensory neuropathy documented in the literature, our patient experienced bilateral lower limb motor weakness following voriconazole administration.

This case underscores the importance of recognizing and monitoring for potential adverse effects of voriconazole, particularly in patients with predisposing comorbidities. Further research is needed to elucidate the underlying mechanisms of voriconazole-induced neuropathy and to develop strategies for prevention and early detection.

Additionally, efforts should be made to establish grading systems for triazole-induced neuropathy to aid in early diagnosis and management.

References:

[1] Aksoy F, Akdogan E, Aydin K, Yilmaz M, Altunayoglu V, Sozen Ee, Et Al. Voriconazole-Induced Neuropathy. Chemotherapy. 2008;54(3):224–7.

[2] Patterson Tf, Thompson Gr, Denning Dw, Fishman Ja, Hadley S, Herbrecht R, Et Al.Practice Guidelines For The Diagnosis And Management Of Aspergillosis: 2016 Update By The Infectious Diseases Society Of America. Clin Infect Dis Off Publ Infect Dis Soc Am. 2016 15;63(4):E1–60.

[3] Hayes Ge, Novak-Frazer L. Chronic Pulmonary Aspergillosis-Where Are We? And Where Are We Going? J Fungi Basel Switz. 2016 Jun 7;2(2).

[4] Tsiodras S, Zafiropoulou R, Kanta E,Demponeras C, Karandreas N, Manesis Ek.Painful Peripheral Neuropathy Associated With Voriconazole Use. Arch Neurol. 2005 Jan;62(1):144–6.

[5] Lewis Re. Pharmacodynamic Implications For Use Of Antifungal Agents. Curropin Pharmacol. 2007 Oct;7(5):491–7.

[6] Lin Mj-Y, Paul Mr, Kuo Dj. Severeneuropathic Pain With Concomitantadministration Of Vincristine And Posaconazole. J Pediatr Pharmacolther Jppt Off J Ppag. 2018 Oct;23(5):417–20.

[7] Baxter Cg, Marshall A, Roberts M, Feltontw, Denning Dw. Peripheral Neuropathy In Patients On Long-Term Triazole Antifungal Therapy. J Antimicrob Chemother. 2011 Sep;66(9):2136–9.

[8] Bradley Wg, Karlsson Ij, Rassol Cg.Metronidazole Neuropathy. Br Med J. 1977 Sep 3;2(6087):610–1.

[9] Hayes Ge, Novak-Frazer L. Chronic Pulmonary Aspergillosis-Where Are We? And Where Are We Going? J Fungi Basel Switz. 2016 Jun 7;2(2).

[10] Hussain S, Nissen S, Holland Sm, Sandronip, Lionakis Ms. Treatment Of Posaconazole-Induced Peripheral Neuropathy With Methylprednisolone And Magnesium Infusions: A Case Report. Open Forum Infect Dis [Internet]. 2019 Feb 1 [Cited2019 Mar 22];6(2). Available From: Https://Academic.Oup.Com/Ofid/Article/6/2/Ofz031/53639 01.