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Autonomic Dysfunction Induced by Single Cycle Combination Therapy with Paclitaxel-Cisplatin

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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) involving the autonomic nervous system (ANS) is frequently reported in the literature next to somatic sensory neuropathies. A few chemotherapy agents, such as platinum-based compounds and taxanes, are known to cause dose-dependent cumulative neurotoxicity, wherein autonomic symptoms develop gradually throughout treatment. However, when these chemotherapeutic agents are administered together as a part of a chemotherapy regimen, possible synergistic neurotoxicity is anticipated, even with a single course of treatment. We described a patient who developed severe autonomic dysfunction resulting in neurogenic orthostatic hypotension (nOH) and paralytic ileus after receiving only a single course of paclitaxel-ifosfamide-cisplatin (TIP) regimen for recurrent testicular cancer. The patient was bedridden for six weeks with slow recovery and remained with nOH for three months after discharge. Monitoring ANS parameters (blood pressure, heart rate, and their alterations upon standing) and timely identification of autonomic dysfunction is crucial to introducing treatment modifications/cessations accordingly.

Keywords: *nocturnal orthostatic hypotension, autonomic dysfunction, cisplatin, paclitaxel*

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1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) involving the autonomic nervous system (ANS) is frequently reported in the literature next to somatic sensory neuropathies. [1,2,3,4] A few chemotherapy agents such as platinum-based compounds and taxanes are known to cause dose-dependent cumulative neurotoxicity, where autonomic symptoms develop gradually over the course of treatment. [1,2] However, when these chemotherapeutic agents are given together as a part of a chemotherapy regimen, possible synergistic neurotoxicity is anticipated even with a single course of treatment.

We described a patient who received a cisplatin-ifosfamide-paclitaxel (TIP) regimen as salvage therapy for recurrent non-seminomatous germ cell tumors of the testis. [5,6] The patient developed severe dysautonomia involving parasympathetic division of cardiac and enteric systems, manifesting as severe debilitating neurogenic orthostatic hypotension (nOH) and paralytic ileus with a single course.

2. Case report

The patient is a 44-year-old man with recurrent disseminated non-seminomatous germ cell tumour of the left testis and was admitted to receive salvage chemotherapy with TIP protocol. He received paclitaxel: 175 mg/m2, ifosfamide: 1500 mg/m2, cisplatin: 25 mg/m2 on day 1 followed by ifosfamide: 1500 mg/m2 and cisplatin: 25 mg/m2 on days 2-5 with appropriate hydration. On day 5 of chemotherapy, he experienced a near-syncopal episode while standing. On initial examination, the lying blood pressure (BP) was 137/80 mm Hg, and the heart rate (HR) was 92 beats/min; on immediate standing, the BP dropped to 76/54 mm Hg, and the HR was 101 beats/min; and after 3 minutes of standing, BP was 69/49 mm Hg, and HR was 102 beats/min, suggestive of neurogenic orthostatic hypotension (nOH). A similar episode occurred on day six. 24-hour BP tracing showed nocturnal supine hypertension (NSH) (Figure 1).

The examination was suggestive of diminished sensation to pain, temperature, vibration and/or proprioception, and loss of deep tendon reflexes in bilateral lower extremities. No abnormalities in levels of cortisol, adrenocorticotropic hormone (ACTH), catecholamine levels, free thyroxine (FT4), thyroid-stimulating hormone (TSH), hemoglobin A1C, vanilylmandelic acid (VMA), antidiuretic hormone (ADH), electrocardiogram, or brain magnetic resonance imaging scan were detected. Cerebrospinal fluid (CSF) analysis was negative for paraneoplastic antibodies. Abdominal x-ray was suggestive of non-obstructive paralytic ileus (Figure 2).

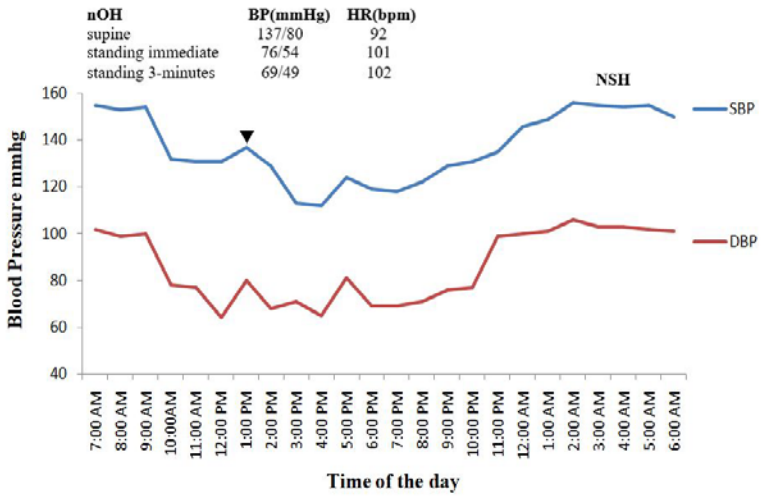

Figure 1. Blood Pressure variability in a patient with autonomic dysfunction leading to nOH (black arrow head) and nocturnal supine hypertension. Abb: nOH-nocturnal orthostatic hypotension; BP- blood pressure; HR- heart rate; bpm-beats per minute

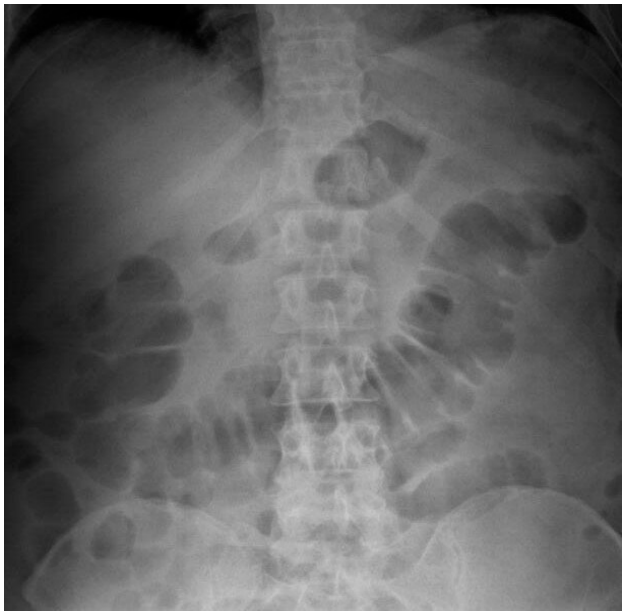

Figure 2. Abdominal X-ray showing air-filled small and large bowel loops suggestive of paralytic ileus

After extensive workup, it was determined that the patient developed drug-induced autonomic failure due to cisplatin and paclitaxel-induced neurotoxicity. Further scheduled cycles of TIP were discontinued. Pressure support medications such as midodrine or fludrocortisone could not be given due to NSH necessitating non-pharmacological interventions such as abdominal binders and compression stockings. The patient was bedridden for 6 weeks with slow recovery. He was able to walk with assistance with cane after 3 months of discharge. He continued to be nOH based on orthostatic vital signs, however the NSH was resolved. He was started on midodrine 10 mg twice a day and he was able to ambulate independently 8 months after the discharge with negative orthostatic vital signs.

3. Discussion

We described a patient who developed nOH due to autonomic failure caused by synergistic paclitaxel and cisplatin-induced neurotoxicity.

Although uncommon, evidence of CIPN involving ANS due to cisplatin and paclitaxel is limited to case reports with unknown incidence. [1,2] The neurotoxicity occurs in a dose-dependent manner. The higher cumulative doses exceeding 1,400 mg/m2 for paclitaxel, and 350 mg/m2 for cisplatin are known to cause autonomic dysfunction which includes nOH, paralytic ileus and cardiac arrhythmia. [3,7,8] Our patient developed autonomic dysfunction with one single low dose of 175 mg/m2 of paclitaxel and a cumulative dose of 100 mg/m2 of cisplatin, which is way less than what was described in the literature. This could be due to concomitant administration of both cisplatin and paclitaxel, whose synergistic neurotoxicity might have induced autonomic dysfunction. M. Vassilomanolakis et al. [1] reported a patient who developed OH with a concomitant single dose of paclitaxel (135 mg/m2) and cisplatin (75 mg/m2). In addition, the risk of developing CIPN is

greater in patients with preexisting conditions that may cause neuropathy (such as diabetes or kidney disease). [3,7,8] However, our patient did not have these underlying co-morbidities. Recently, studies have been conducted to quantify the autonomic dysfunction induced by chemotherapy. A study conducted by Dermitzakis et al. [3] showed significant autonomic dysfunction involving parasympathetic division predominantly manifesting in nOH in 20% of the patients. Interestingly, nOH was resolved after the end of treatment suggesting that the autonomic dysfunction is short-lived. However, in our patient, nOH was severe and remained for three months post-treatment with slow recovery. Our patient also developed mild paralytic ileus suggesting the enteric parasympathetic nervous system involvement. Jiao et al. [9] described a patient who developed similar symptoms of paralytic ileus due to nab-paclitaxel toxicity.

nOH is the hallmark of autonomic neuropathy which is defined as a sustained decrease in systolic BP ≥20 mmHg or diastolic BP ≥10 mmHg within 3 minutes of standing with little or no accompanying increase in HR (<15 bpm). [10] In addition to nOH, other clinical manifestations suggestive of autonomic neuropathy include NSH, resting tachycardia, and non-dipping of nocturnal blood pressure. [10,11] These can be identified with 24-hour ambulatory BP monitoring, which can be used as a tool for diagnosing autonomic dysfunction in the absence of specific tests such as head up tilt-table test, BP response to valsalva, and heart rate response to deep breathing (HRDB). [11] Unfortunately, our patient did not get any specific autonomic testing due to limited access to autonomic lab testing and delayed appointment. Our patient was confirmed to have autonomic dysfunction based on the clinical manifestations, positive orthostatic vital signs suggestive of nOH and NSH.

Neurotoxicity from cisplatin is speculated to result from inhibition of DNA repair pathways, leading to apoptosis and mitochondrial injury [7], whereas paclitaxel predominantly causes microtubule injury. [7,8] After extensive workup to rule out other causes of autonomic dysfunction including paraneoplastic processes, it was determined that the patient developed CIPN involving ANS, given the timeline of presentation. However, it is unclear why our patient developed severe autonomic dysfunction only with a single course. Perhaps, individual factors such as genetic influences on DNA repair and drug transport mechanisms might have played a role.

4. Conclusions

The present case highlights the fact that synergistic paclitaxel and cisplatin chemotherapy can result in severe, long-lasting and morbid nOH even with a single course of treatment. Monitoring of ANS parameters (BP, cardiac rhythm and their alterations upon standing) and timely identification of autonomic dysfunction is important to introduce treatment modifications/cessations accordingly.

Acknowledgements

none.

Statement of Competing Interests

The authors have no competing interest.

List of Abbreviations

CIPN: Chemotherapy-induced peripheral neuropathy, ANS: autonomic nervous system, nOH: neurogenic orthostatic hypotension, TIP: paclitaxel-ifosfamide-cisplatin, BP: blood pressure, HR: heart rate, NSH: nocturnal supine hypertension, ACTH: adrenocorticotropic hormon, TSH: thyroid-stimulating hormone, VMA: vanillyl mandelic acid, ADH: antidiuretic hormone, CSF: Cerebrospinal fluid, HRDB: heart rate response to deep breathing.

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