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CASE REPORT

Seizure related paclitaxel and carboplatin infusion in breast cancer patient

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ABSTRACT

Seizure is a common symptom of brain tumors, whether they are primary or metastatic. Seizure in patient with breast cancer can sometimes occur for reason unrelated to tumor, such as metabolic encephalopathy, cytotoxic chemotherapy, paraneoplastic syndromes, cranial irradiation and stroke related to cancer. Many chemotherapeutic agents also reported cause seizures (paclitaxel, cisplatin, 5- fluorouracil, methotrexate and cyclosporine). We present a case of 45-years-old female who experienced an acute seizure shortly after receiving an infusion of Paclitaxel and Carboplatin for grade 3 ductal breast cancer. This rare adverse drug reaction should increase the physicians and pharmacist in treating cancer patients.

Keywords: seizure, acute symptomatic, paclitaxel, carboplatin, breast cancer

INTRODUCTION

Breast cancer is the second most common cause of death among women in the United States, with 287,850 new cases in 2022 and 43,250 deaths from breast cancer that year [1]. Breast cancer can metastasize to various organs, such as the bones, lungs, liver, and brain. There are 24% of breast cancer cases that metastasize to the brain. Despite this, data on the incidence of seizures in breast cancer patients with brain metastases is limited [2]. A review of 106 studies found that 12% of breast cancer patients with brain metastases experienced seizures. Other studies have indicated that chemotherapy agents may have epileptogenic properties, meaning it can trigger seizures, with examples including methotrexate, fludarabine, vincristine, cisplatin, cytarabine, and etoposide, as well as other drugs prescribed for cancer patients (tricyclics,

clozapine, bupropion, penicillin, and phenothiazines) [3].

Brain metastasis is a common complication in metastatic breast cancer, particularly in advanced stages (Stage IV), where cancer cells from the primary breast tumor spread to other body parts via the bloodstream or lymphatic system. It is estimated that 10-16% of patients with advanced breast cancer develop brain metastasis, with the likelihood varying depending on the breast cancer subtype. Breast cancer is a diverse disease, the specific subtype a patient has significantly influences the risk of developing brain metastasis. Subtypes like triple-negative and HER2-positive breast cancers are more likely to lead to brain metastasis. In contrast, tumors positive for hormone receptors, especially estrogen receptor-positive (ER+), generally have a lower risk of brain metastasis compared to hormone receptor-negative tumors [4].

The mechanism of brain metastasis in breast cancer can involve several pathways, including hematogenous spread, where tumor cells travel through the bloodstream aided by the tumor's vascularity and cell adhesion molecules, as well as lymphatic spread, and infiltration through the blood-brain barrier. HER2 is a critical protein that plays a role in cell growth and division. In certain breast cancers, overexpression of HER2 can occur, making these cancer cells more aggressive and increasing their likelihood of metastasizing, including to the brain [5]. HER2-positive breast cancers are known to grow more rapidly and carry a higher risk of brain metastasis. This increased risk is due to the overexpression of HER2, which not only promotes aggressive primary tumor growth but also enhances the tumor's ability to invade the bloodstream, making it more likely for cancer cells to reach and metastasize to the brain [6].

The clinical presentation of brain metastasis in breast cancer patients can vary, including seizures, headaches, neurological deficits, cognitive changes, visual disturbances, behavioral and personality changes, nausea, and vomiting. Neurological examinations are essential for evaluating clinical symptoms and neurological function, helping to detect any deficits or abnormalities that may result from brain metastasis [7]. Radiological imaging, including MRI and CT scans, serves as the primary diagnostic method for detecting brain metastasis. On these images, brain metastases typically present as contrast-enhancing masses, a result of the disrupted blood-brain barrier around the metastatic lesion, which allows contrast agents to accumulate in the tumor. Radiological imaging is also vital for distinguishing metastatic brain tumors from primary brain tumors and identifying the presence of multiple metastatic lesions in the brain [8]. Radiological imaging can also detect peritumoral edema, swelling, and inflammation in the brain tissue surrounding a metastatic lesion. This edema typically appears as an area of increased signal intensity on MRI scans. MRI is considered the gold standard for brain imaging,

particularly in detecting and characterizing brain metastasis, as it is capable of visualizing small or multiple lesions, determining their precise location, and assessing their relationship with surrounding brain structures. On the other hand, CT scans are useful for identifying large, calcified, or hemorrhagic brain metastases [9].

Seizures are common in cancer patients, with brain metastases being the leading cause in adults. These metastases often originate from the skin, breast, lungs, kidneys, and colon, with approximately 70% annually coming from the lungs orb breast [10]. The frequency of seizures differs based on the type of brain neoplasm. Cancer patients are at an elevated risk for seizures due to several factors that are not directly related to the tumor, including cytotoxic chemotherapy, metabolic encephalopathy, paraneoplastic syndromes, cranial irradiation, and strokes linked to cancer. Additionally, various chemotherapeutic agents can also trigger seizures [11,12]. Patients with systemic cancer have a generally higher incidence of epilepsy. Seizures are prevalent among cancer patients, affecting up to 60% of those with brain metastasis. This situation necessitates the use of anticonvulsant medications in conjunction with antitumor treatments like chemotherapy. However, combining these therapies can significantly increase the risk of drug interactions, with brain tumor patients experiencing a six-fold higher risk compared to those with systemic cancer. Pharmacokinetic between drugs interactions can occur due to alterations in the absorption, distribution, metabolism, or elimination of medications. Chemotherapy agents and tyrosine kinase inhibitors can influence the pharmacokinetics of other treatments administered concurrently. Using anticonvulsants (AEDs) in combination with chemotherapy or tyrosine kinase inhibitors involves a risk of drug-drug interactions (DDIs). These drug classes can stimulate enzyme activity, and tyrosine kinase inhibitors may also enhance the toxicity of other drugs by inhibiting enzyme function [13].

Enzyme-inducing anticonvulsants (EIAEDs) can enhance the clearance of chemotherapy drugs that are metabolized concurrently by about two to three times, affecting medications such as cyclophosphamide, irinotecan, paclitaxel, and teniposide. The clearance can increase up to four times faster when combined with tyrosine kinase inhibitors like lapatinib, imatinib, dasatinib, imatinib, and crizotinib. Moreover, tyrosine kinase inhibitors, especially imatinib and crizotinib, can lead to the inhibition of enzymes that are crucial for the metabolism of other treatments. Many newer anticonvulsants do not affect drug metabolism but can alter enzyme activity through interactions with different medications, such as other anticonvulsants, chemotherapy drugs, and tyrosine kinase inhibitors. Furthermore, glucocorticoids can induce metabolic changes as well. Consequently, these interactions can lead to drug toxicity unless dose

adjustments are implemented [13].

Paclitaxel is a chemotherapeutic agent used for various types of cancer. Indications for paclitaxel use include breast cancer, ovarian cancer, bladder cancer, lung cancer, prostate cancer, and various other solid tumors [14]. The therapeutic effects of taxanes (paclitaxel) are due to the blockade of microtubule depolymerization, which leads to the inhibition of cell division. The antiproliferative effects of platinum-based drugs (carboplatin) result from DNA-protein and between DNA cross-linking, leading to the blockage of DNA replication and/or repair [15]. Paclitaxel works by inhibiting cancer cells from multiplying into new cells, thereby inhibiting cancer growth. Carboplatin is activated within the cell and forms reactive platinum complexes that cause cross-linking of DNA molecules within the cell. This results in structural changes to the DNA and inhibits DNA synthesis, which can affect cell death, particularly in rapidly dividing cells [16].

Carboplatin, an antineoplastic medication, belongs to the class of platinum-based agents and is categorized as an alkylating agent. It exerts its effects through several mechanisms: (1) by transferring alkyl groups to guanine residues in DNA, leading to DNA fragmentation and the creation of mismatched bases, and (2) by forming interstrand or intrastrand cross-links, which cause DNA damage and hinder the separation of strands during DNA synthesis or transcription [17]. Carboplatin and paclitaxel may both induce nerve toxicity as a side effect, often manifesting as azonal sensory peripheral neuropathy. Although neurotoxicity affecting the central nervous system, like acute seizures is uncommon, there have been past reports linking these drugs to seizures, cortical blindness, aphasia, hemiparesis, and coma [18].

We report the case of a 45-year-old woman diagnosed with ductal breast carcinoma who experienced a seizure shortly after receiving an infusion of paclitaxel and carboplatin. Her laboratory tests returned normal results, and a CT scan of the brain showed no signs of primary metastasis or meningeal carcinomatosis. She had no infection symptoms, history of seizures, fever or medication that might predispose her to such an event. After eliminating other potential causes, the seizure was most likely attributed to the chemotherapy, with carboplatin and paclitaxel being the probable agents due to their temporal association with the adverse event.

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CASE PRESENTATION

A 45-year-old woman who had received first time chemotherapy after mastectomy for ductal carcinoma of the breast was referred to emergency department. She came with general tonic-clonic seizure after 10 minutes infusion of paclitaxel 210 mg and carboplatin 300 mg. The premedication were ondansetron 8 mg, one ampule of ranitidine, and one ampule of 4 mg Dexamethasone. During the seizure, she exhibited up-rolling of the eyeballs and tongue biting. She was sedated with intravenous diazepam and started on phenytoin. After the seizure, she showed signs of confusion, drowsiness, and slurred speech.

A neurology examination confirmed a diagnosis of simple partial seizure with secondary generalization. Electroencephalography (EEG) revealed abnormally activity, including sharp waves and a slowing pattern. A computed tomography (CT) scan of the brain revealed no focal lesions. Laboratory tests, including complete blood counts, renal function tests, blood glucose levels, liver function tests, and serum electrolytes (calcium, chloride, potassium, sodium, and magnesium), were all within normal ranges. Additionally, the chest X-ray, electrocardiography, and two-dimensional echocardiogram were normal. The patient's blood pressure remained stable before, during, and after chemotherapy. There were no complaints of fever or signs of sepsis.

At the times of discharged, she was fully alert, no seizure, and independent. Two weeks later, she reported no neurological complaints. She continued receiving phenytoin injections for three days without any further seizure episodes. Upon discharge, she was prescribed oral phenytoin and levetiracetam.

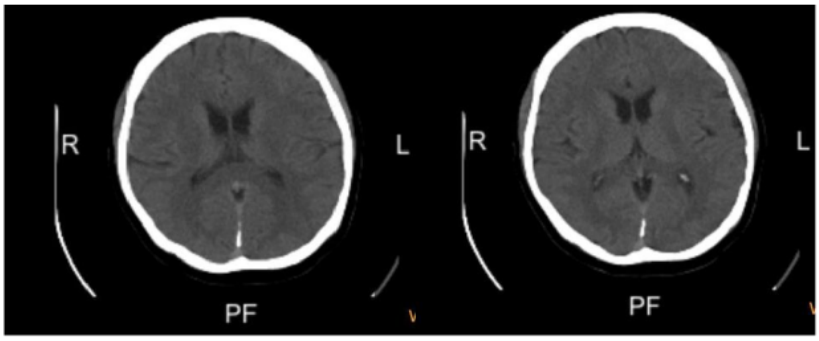

FIGURE 1. The brain CT scan of the patients, rule out brain metastases

DISCUSSION

Seizures in cancer patient can result from primary and metastatic brain tumors, paraneoplastic syndromes, or treatment-related factors such as radiation therapy, chemotherapy, and other drugs like antibiotics and narcotics. Seizures occur in less than 1% of patients treated with systemic chemotherapy. Chemotherapy, which uses strong biological agents, can cause significant negative effects on the body. Platinum- based drugs are considered first-line cytotoxic treatments for several cancers, but it's also associated with neurotoxicity [19]. Platinum-based drugs often lead to peripheral sensory neuropathy because they more easily penetrate the dorsal root ganglia and peripheral nerves compared to the brain, which has limited permeability due to the blood-brain barrier. Common toxic effects include hypokalemia, hypocalcemia, and hypomagnesemia [20].

Several previous reports showed the nervous system toxicity either with paclitaxel or carboplatin. Cases of transient cortical blindness, seizures, and posterior reversible encephalopathy syndrome (PRES) have been documented [20,21]. On a CT scan, Posterior Reversible Encephalopathy Syndrome (PRES) is characterized by the presence of subcortical vasogenic edema and notable white matter lesions in the parieto-occipital areas. Although the clinical signs and symptoms are non-specific, common manifestations include headaches, seizures, altered mental status, and visual disturbances, often accompanied by hypertension. Chemotherapy agents linked to PRES comprise taxanes, immunosuppressants, folate antagonists, angiogenesis inhibitors, anthracyclines, platinum derivatives, vinca alkaloids, and antimetabolites. In PRES, a rapid increase in hypertension exceeds the limits of cerebral blood flow autoregulation, resulting in hyperperfusion that disrupts the blood-brain barrier and allows plasma and macromolecules to leak into the interstitial space [22].

A case of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) was documented in a lung cancer patient from Japan, suspected to be linked to vascular endothelial toxicity resulting from a carboplatin and paclitaxel regimen. RPLS is characterized by symptoms such as headaches, altered consciousness, seizures, visual disturbances, and changes in both white and gray matter indicative of cerebral edema, particularly affecting the posterior regions of both cerebral hemispheres, especially the parieto-occipital areas. This syndrome frequently occurs as a complication of chemotherapy due to its toxic effects on the central nervous system (CNS). Seizures may present at the onset of neurological symptoms and can start focal. The mechanism behind RPLS is characterized by cerebral vasogenic edema linked to hypertension and brain capillary leak syndrome, along with compromised vascular autoregulation. Additionally, the cytotoxic effects of immunosuppressive and chemotherapeutic drugs on the vascular endothelium

can contribute to the disruption of the blood-brain barrier. Reports have indicated that platinum analogs can occasionally induce CNS toxicity [23].

Encephalopathy, both acute and late-onset, has been observed with paclitaxel, although some cases involved underlying brain metastasis, prior radiotherapy to the brain, disruption of the blood-blain barrier, or brain surgery. Seizures shortly after paclitaxel infusion initiation have been reported, with one case describing hypersensitivity symptoms like chest tightness and flushing followed bye a generalized tonic-clonic seizure within 5 minutes of infusion. However, in our patient, the paclitaxel infusion proceeded without incident. Cremophor, a solvent for paclitaxel, is also known as a neurotoxic agent with procoagulant effects that can cause thrombotic-embolic events. Cremophor is a formulation ingredient containing surfactants used for various poorly water-soluble drugs, including paclitaxel [23]. Paclitaxel, a potent antimitotic agent, stabilizes and prevents microtubule depolymerization by targeting tubulin. It has broad antitumor activity with side effects including myelosuppression and peripheral neurotoxicity, but central nervous system (CNS) toxicity following IV administration is rarely reported [24].

Clinical observations have shown that paclitaxel can mitigate the antiplatelet toxicity of carboplatin when the two drugs are combined, although the antitumor activity and white blood cell toxicity are additive. This effect is due to the interaction between the two drugs at the platelet precursor level [25]. The pairing of carboplatin and paclitaxel shows antagonistic interactions when tumor cells are treated with carboplatin before paclitaxel or when both drugs are given at the same time. However, minimal antagonism is observed when paclitaxel is given before carboplatin. Administering paclitaxel (Taxol) alongside carboplatin has shown advantages; a 1996 study indicated that this combination is more effective for treating advanced-stage ovarian cancer while presenting lower toxicity compared to the Taxol and cisplatin combination. The cisplatin- Taxol group experienced significantly higher rates of gastrointestinal, renal, metabolic toxicities, and leukopenia compared to those treated with the carboplatin-Taxol combination. Toxic side effects, such as nausea and weight loss, were also less frequent with carboplatin-Taxol. Additionally, carboplatin-Taxol can be safely and effectively administered over a 3-hour infusion period, whereas cisplatin-Taxol requires a 24-hour infusion, necessitating hospitalization [26].

However, paclitaxel must be administered before carboplatin because if carboplatin is given first, paclitaxel (Taxol) will not exert its effects on cancer cells. Research indicates that previous or simultaneous treatment with carboplatin can hinder Taxol-induced degradation of I-kappa, B-alpha, and phosphorylation of BCL-2. Additional analysis indicated that carboplatin

notably disrupts the cytotoxic effects of paclitaxel on mitotic arrest and apoptotic cell death, unless paclitaxel is given before carboplatin. Additional studies have shown that the interaction between paclitaxel and carboplatin is is heavily dependent on the sequence of administration, with the most effective results occurring when paclitaxel is given first, followed by carboplatin [26].

An algorithm for diagnosing chemotherapy-induced seizures was established using the WHO-UMC causality assessment system, considering: (1) onset of encephalopathy shortly after chemotherapy infusion; (2) exclusion of other physical or metabolic factors that could trigger seizures; (3) absence of concurrent administration of other drugs or analgesics; and (4) response to withdrawal [26, 27]. Platinum-based chemotherapeutic agents are considered a first-line cytotoxic treatment option for various cancers, including lung, colorectal, ovarian, bladder, testicular, and breast cancers. Due to their cytotoxic nature, these agents are not free from side effects, one of which is electrolyte disturbances, particularly hypomagnesemia. This is most commonly seen with cisplatin (10%-90%) and with carboplatin at around 10%. The neurological consequences of hypomagnesemia may encompass seizures, vertigo, ataxia, nystagmus, athetosis, and choreiform movements. Additionally, nephrotoxicity is a recognized adverse effect of platinum-based agents, with a reduction in magnesium levels considered an early sign of cisplatin-induced kidney damage, while a rise in creatinine levels typically indicates a later stage of injury [27].

It is proposed that platinum agents are filtered through the glomerulus, with cisplatin being significantly more filtered than carboplatin or oxaliplatin, which are mainly attached to plasma proteins. These agents subsequently access renal tubular cells through organic cation transporters, resulting in nephrotoxicity and disrupting magnesium reabsorption in the ascending loop of Henle and the distal tubules. Furthermore, proton pump inhibitors (PPIs) are known to induce hypomagnesemia that does not respond to oral magnesium supplementation and can also trigger tonic-clonic seizures. It is suspected that PPIs increase luminal pH in the intestine, which diminishes the affinity of magnesium influx channels (Transient Receptor Potential Melastatin 6, TRPM6/7) for magnesium absorption [27].

In our patients, other causes of encephalopathy were ruled out by neuroimaging and blood serum examination. The strongest evidence for our hypothesis is provided by the fact that a seizure occur shortly after the infusion without any other possible causes. Carboplatin appears to be the more likely culprit based on the temporal relationship between its administration and the seizure. However, we cannot completely dismiss paclitaxel as a potential contributing factor

[28].

CONCLUSION

We present a rare case of seizure induced by carboplatin and paclitaxel infusion. Platinum-based agents like carboplatin and paclitaxel can induce neurotoxicity and electrolyte disturbances such as hypomagnesemia, which may contribute to seizures. An algorithm based on WHO-UMC causality assessment criteria helps diagnose chemotherapy-induced seizures. While seizures triggered by chemotherapeutic agents are uncommon and can be caused by various factors, it's crucial for physicians and pharmacists to be aware of this potential adverse drug reaction.

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