

SEVERE, DISABLING NEUROLOGIC TOXICITY FOLLOWING CISPLATIN RETREATMENT

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OBJECTIVE: To describe a severe neurotoxic reaction following the second cycle of cisplatin-based chemotherapy.

CASE SUMMARY: A patient with unresectable non-small-cell lung cancer was treated with combined chemotherapy and radiotherapy. Thirty-six hours after the second course of chemotherapy, the patient developed severe mental status changes consisting of aphasia, confusion, and agitation. Complete neurologic workup was most consistent with an acute vascular event.

DISCUSSION: Reports of acute cisplatin-induced neurologic toxicity involving the central nervous system are rare. Potential risk factors are described. Mechanisms of chemotherapy-induced vascular damage are discussed.

CONCLUSIONS: Total dosage and administration schedule of cisplatin are associated with an increased incidence of neuropathy. However, factors predicting the development of early, acute neurotoxicity are limited by the rarity of these events. It is probable that acute neurotoxic reactions in cancer patients are caused by an unknown complex of interactions involving drugs, tumor, and host factors.

Ann Pharmacother 1995;29:134-7.

THE SUCCESS OF A NUMBER of chemotherapy regimens for germ-cell tumors, ovarian cancer, small-cell lung carcinoma, and osteosarcoma can be attributed, in part, to cisplatin. Hence, the drug's broad spectrum of antitumor activity is now better used. Precautions and improved supportive therapy with vigorous intravenous hydration and antiemetics can ameliorate cisplatin's potentially severe, dose-limiting renal and gastrointestinal toxicity.^{1,2} Presently, polyneuropathy is another treatment-limiting adverse effect of cisplatin.³⁻⁵ Sensory neuropathy has developed in more than half of the patients treated with this agent, depending on the dose and method of administration.⁶⁻⁸ Cisplatin neuropathy is a cumulative, dose-related phenomenon, with patients usually becoming symptomatic after receiving more than 300 mg/m².³ However, there is a broad range of doses (100-600 mg/m²) in which neurotoxic effects have occurred.^{3,9}

Rare instances of encephalopathy, cranial neuropathy, seizures, and cerebrovascular accidents have been described following intravenous or intracarotid cisplatin.¹⁰⁻¹³ These reported cases lacked other significant risk factors

for neurologic toxicity, with the exception of a few patients with brain tumors. We describe a patient who developed a severe, debilitating central nervous system toxicity following a second course of cisplatin therapy.

CASE REPORT

An unresectable adenocarcinoma of the lung was diagnosed in a 40-year-old woman in January 1994. Except for left hilar and mediastinal adenopathy, there were no other focal areas of metastatic disease. Plain film X-rays revealed findings consistent with her history of hypertrophic osteoarthropathy. Computed tomography (CT) of the head was normal. Her neurologic examination also was completely normal before she began combined modality therapy in early February with cisplatin (80 mg/m² iv over 2 h × 1 dose, without mannitol), etoposide (80 mg/m²/d iv over 2 h × 3 doses), and concomitant radiation to the chest. Approximately 10 days later, her husband reported that the patient began experiencing intermittent episodes of confusion and partial loss of motor coordination involving her hands and legs.

The patient was admitted to the hospital on February 28 for a second cycle of chemotherapy. CT scan of the head on the day of admission showed several small lesions bilaterally in the parietal-occipital lobes; these were assessed by the radiologists and neurosurgeons to be atypical of metastases. Magnetic resonance imaging (MRI) of the head performed on March 2 showed focal areas of increased signal intensity; this was suggestive of either an embolic vascular accident or vasculitis, although metastases or infection could not be excluded (Figure 1A). Chemotherapy was completed on March 2 without complications. A lumbar puncture was ordered prior to discharge, but could not be performed. The patient was clinically stable on discharge and had a return visit scheduled in 1 week.

Approximately 36 hours after the cisplatin infusion, the patient's husband found her to be verbally unresponsive, confused, and agitated. The patient was brought to the emergency department and admitted. Initial examination revealed a disorganized and combative middle-aged woman. Her T was 37.5 °C, HR 120 beats/min, RR 20 breaths/min, and BP 140/80 mm Hg. Physical examination revealed ocular movement that did not progress past midline to the left; there was no nystagmus. The left eye was negative for papilledema; funduscopy could not be performed on the right eye. Cardiac examination was normal. The lungs were clear to auscultation except for decreased breath sounds at the left base.

On neurologic examination, the patient was disoriented to time, place, and person, although expressive aphasia was present. Her lack of cooperation made assessment of motor function difficult. Sensory examination for pain remained intact. Deep tendon reflexes were 3+ and symmetric. Ankle and patellar clonus was present. Plantar response was upgoing bilaterally.

The white blood cell count was 11.4 × 10⁹/L with polymorphonuclear cells 0.95 fraction of 1.00. The platelet count, hemoglobin, and hematocrit were 73 × 10⁹/L, 120 g/L, and 0.36 fraction of 1.00, respectively. Except for a creatinine of 141 μmol/L, electrolyte concentrations were normal. Laboratory evaluation also revealed negative findings for both antinuclear antibodies and rheumatoid factor, an erythrocyte sedimentation

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rate of 23 mm/h, fibrinogen of 2.2 g/L (normal 2.0–4.0), which decreased to 1.2 g/L a week later, and a prothrombin time of 14 s, which peaked at 16.5 s 5 days later.

A transesophageal echocardiogram showed no vegetation on the aortic or mitral valves. A repeat MRI scan on March 4 indicated development of bilateral cortical areas with increased signals involving predominantly gray matter (Figure 1B). A cerebral arteriogram demonstrated changes in the right midcerebral artery consistent with arteritis, although embolic phenomena could not be excluded. Electroencephalogram was normal. A lumbar puncture revealed normal opening and closing pressure. Analysis of the cerebrospinal fluid (CSF) showed glucose of 4.7 mmol/L, protein content of 0.39 g/L, many red blood cells (consistent with a traumatic tap), and 2 white blood cells. Culture of the CSF was negative for bacteria and fungi. A micropore membrane analysis was negative for malignant cells.

Empiric antibiotic therapy was started to treat a possible meningococcal infection. A loading dose of phenytoin, with daily doses to maintain a therapeutic concentration, and dexamethasone 16 mg/d were also initiated.

After reviewing the results of the patient's studies, neurology consultants believed the patient's condition was the result of an embolic process, although vasculitis could not be completely ruled out. The patient's condition improved slowly but steadily. By hospital day 7 she had become more oriented and less agitated. However, the patient was still unable to verbalize simple sentences. By hospital day 10 the patient was ambulating under the guidance of a physical therapist.

Phenytoin was discontinued on day 12. Repeat MRI scan on March 14 showed changes commonly observed in patients with evolving ischemic lesions (Figure 1C).

The patient was hospitalized for 14 days. Although she became oriented, her verbal communication was characterized by perseveration and receptive aphasia. Laboratory results of electrolyte concentration analyses remained normal. Dexamethasone was tapered and discontinued, and the patient was transferred to a rehabilitation hospital for continuing supportive and restorative care. Six months after the development of multiple cerebral infarcts, the patient died, never fully recovering her ability to speak, eat, or walk.

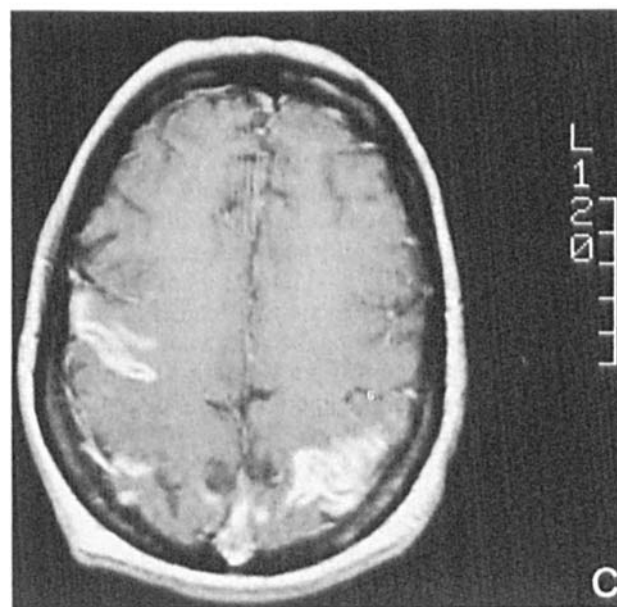
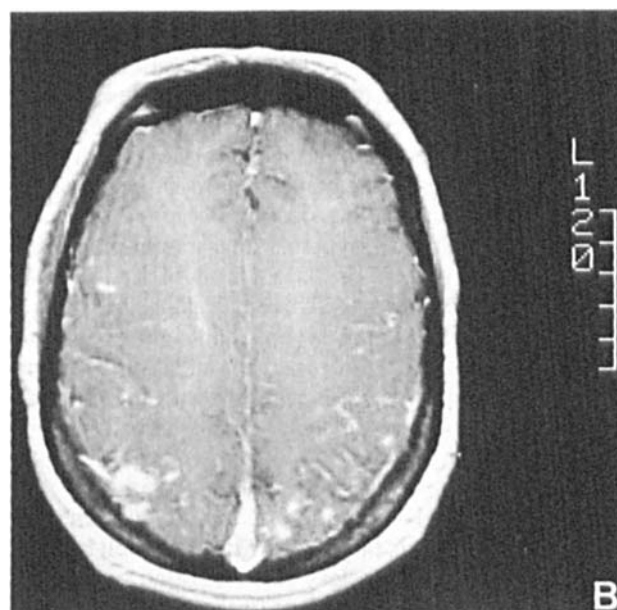
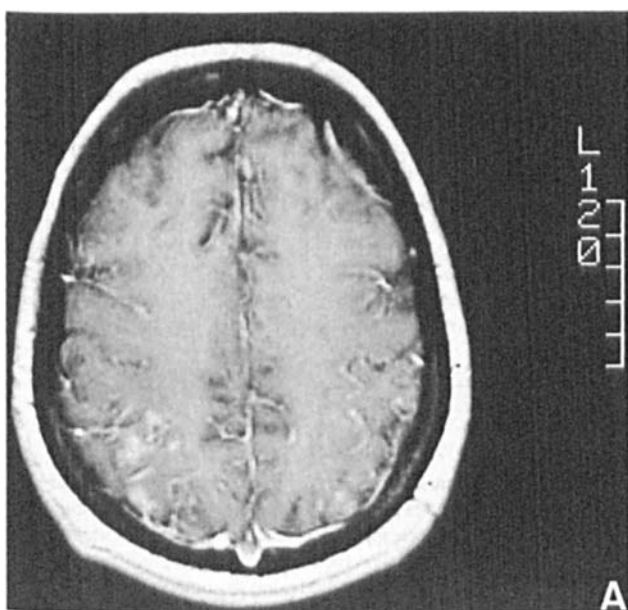


Figure 1. Magnetic resonance images of the head. (A) Focal abnormal areas of signal alteration involving both parietal-occipital lobes. (B) Multiple new large areas of signal alteration along the sulci involving the posterior left temporoparietal lobe and right posterior frontoparietal lobe. (C) The gyriform distribution of small amounts of blood on the brain surface or in the surface cortex strongly suggest an evolving ischemic lesion.

Discussion

The patient described in this report developed a sudden, profound, and progressively debilitating neurotoxic reaction that was temporally related to her second course of cisplatin-based chemotherapy. In view of a negative head CT preceding the patient's initial course of chemotherapy and the atypical cerebral processes found just prior to the second cycle of therapy, it is unlikely that the early signs of labile confusion and mild motor disturbances in the patient can be attributed to brain metastases. In addition, the aggregate findings of the MRI scans, angiogram, and echocardiogram support a vascular rather than metastatic etiology.

Radiographic findings suggestive of embolic infarcts and laboratory parameters indicating disseminated intravascular coagulopathy cannot rule out the possibility that this complication resulted from a thromboembolic process. However, bleeding was not evident either peripherally or centrally.

Although vasculitis, nonbacterial thrombotic endocarditis, and consumptive coagulopathy contribute to cerebrovascular complications in patients with cancer, anticancer agents also have been implicated.^{14,15} A number of possible mechanisms may contribute to the vascular toxicity of cisplatin. Vascular damage from antineoplastic agents has been shown to cause endothelial retraction and increased platelet adhesion.^{16,17} Elevated von Willebrand factor antigen (which was not measured in our patient) also has been found in patients developing acute vascular events.¹⁸ Others have suggested that tumor cell lysis results in a release of proteins that may disrupt the clotting system.¹⁹ Acute cerebrovascular accidents occurring after cisplatin therapy are uncommon. However, it is likely that the development of such events in patients with cancer is the result of a complex interaction of drug, tumor, and host factors.

Neurotoxic reactions associated with etoposide are rare and difficult to assess because many studies use etoposide in combination with other agents, including cisplatin.^{20,21} It is therefore postulated that cisplatin was the responsible factor because of the temporal relationship between its administration and the neurotoxic complication and the absence of other definitive causes.

Dose-dependent peripheral neuropathy, generally seen after 300 mg/m², is one treatment-limiting toxicity of cisplatin.^{3,9} However, acute central neuropathy, presumably vascular in origin, also has occurred at much lower doses even in the absence of hyperosmolar mannitol which can modify the integrity of the blood-brain barrier.¹⁰⁻¹³ In contrast to the patient described herein, it is unclear from previous reports whether the patients had signs or symptoms of mild neurotoxicity prior to cisplatin administration. In these earlier reported cases, central neurotoxic reactions also could have been attributed to fluid overload, electrolyte disturbances, or intracarotid administration of cisplatin, none of which were associated with our patient.¹⁰⁻¹³

Cisplatin-based chemotherapy has had a dramatic impact on the prognosis of patients with germ-cell and ovarian carcinomas. Nevertheless, rare and often severe central neurotoxic reactions can limit further administration of cisplatin.

Summary

Radiologic tests are invaluable diagnostic tools; however, even the most sophisticated procedures contain flaws. It is important to note that clinically overt cisplatin neurotoxicity could masquerade initially as mild central nervous system abnormalities. Clinical signs of difficulty with fine motor coordination, diminished (or loss of) vibratory sensation, or confusion may be indicators of impending, severe central neurotoxic reactions. Because the progression of neuropathy is often unpredictable, a complete neurologic assessment prior to further cisplatin administration is recommended given the uncompromising nature of cisplatin neurotoxicity. ≡

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EXTRACTO

OBJETIVO: Describir un caso clínico de un paciente con cáncer que desarrollo una reacción neurotóxica severa luego de haber recibido un segundo ciclo de quimioterapia con cisplatino. Se revisa la literatura médica y se examinan aquellos factores que pueden predisponer a un paciente a desarrollar este tipo de toxicidad temprano en el tratamiento.

RESUMEN DEL CASO: Un paciente con un tumor de pulmón no resectable fue tratado con una combinación de quimioterapia y radioterapia. Treinta y seis horas luego de haber recibido un segundo curso de quimioterapia, el paciente experimentó cambios mentales severos tales como afasia, confusión mental, y agitación. Un examen neurologico extenso determino que el paciente habia experimentado un evento vascular agudo.

DISCUSIÓN: La cantidad de reportes que describen la toxicidad neurológica causada por cisplatino son escasos. Los factores que predisponen a un paciente a desarrollar esta toxicidad son discutidos en este artículo. El mecanismo por el que ocurre el daño vascular inducido por quimioterapia también son discutidos.

CONCLUSIONES: La dosis total y el horario de administración del cisplatino están asociados con una incidencia aumentada de neurotoxicidad. Sin embargo, aquellos factores que predicen el desarrollo temprano de esta neurotoxicidad aguda no están claramente determinados debido a la baja incidencia de esta reacción. Es posible que estas reacciones neurotóxicas agudas en pacientes con cáncer estén causadas por unas interacciones complejas desconocidas que envuelven el tumor, los fármacos, y los factores de defensa del inmunológico del paciente.

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RÉSUMÉ

OBJECTIF: Décrire une réaction de neurotoxicité sévère chez un patient ayant reçu un second cycle de chimiothérapie incluant le cisplatine. Réviser la littérature et identifier les facteurs prédisposant un patient à cette toxicité précoce.

RÉSUMÉ: Un patient atteint d'un cancer du poumon inopérable reçoit un traitement combiné de chimio et de radiothérapie. Trente-six heures après le deuxième cycle de chimiothérapie, le patient présente une modification sévère de son état mental incluant de l'aphasie, de la confusion, et de l'agitation. Un examen neurologique complet est compatible avec un problème vasculaire aigu.

DISCUSSION: Les cas rapportés de toxicité neurologique induite par le cisplatine, impliquant le système nerveux central, sont rares. Des facteurs de risques potentiels sont décrits. Les mécanismes impliqués dans l'induction de dommages vasculaires par les agents chimiothérapeutiques sont discutés.

CONCLUSIONS: La dose totale et l'horaire d'administration sont des facteurs associés aux phénomènes de neuropathie. Toutefois la rareté des cas de neurotoxicité aiguë rapportés dans la littérature permet difficilement d'identifier les facteurs prédisposants. Il est probable que les réactions neurotoxiques aiguës chez les patients cancéreux sont dues à des interactions inconnues complexes impliquant les médicaments, la tumeur, et le patient.

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