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Cisplatin Neurotoxicity Presenting as Reversible Posterior Leukoencephalopathy Syndrome

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Summary: Visual disturbance, hypertension, convulsions, and unconsciousness developed in a 70-year-old man after cisplatin chemotherapy and upper-limb amputation for osteosarcoma. MR imaging revealed bilateral reversible abnormalities in the occipital, parietal, and frontal white matter. Clinical and neuroradiologic features corresponded to reversible posterior leukoencephalopathy syndrome (RPLS), which some immunosuppressive and chemotherapeutic drugs have been reported to trigger. Cisplatin may be among these drugs. Our patient also had hypomagnesemia, which may have figured in the pathophysiology.

Cisplatin is an anticancer drug used to treat a wide variety of neoplasms. While the most common side effects are nausea and vomiting, nephrotoxicity, myelosuppression, ototoxicity, peripheral neuropathy, and reversible focal cerebral disorders such as seizures and cortical blindness have also been reported (1–4). We describe a patient with reversible white matter abnormalities fulfilling criteria for reversible posterior leukoencephalopathy syndrome (RPLS) (5).

Case Report

A 70-year-old man with no history of epilepsy, renal disease, or hypertension reported pain in his left shoulder. Osteosarcoma was diagnosed in the left upper arm. Ifosmide (2 g/m^2) given as an infusion for 5 days and repeated after 1 month with the addition of etoposide (50 mg/m^2 intravenously for 5 days) had no effect. One month later, cisplatin (50 mg), injected intraarterially in the region of the tumor, selectively reduced its size. The left upper limb was amputated after 23 days of cisplatin therapy. On the evening of the second postoperative day, the patient's blood pressure became asymptomatically elevated (180/100 mm Hg), and on the morning of the third postoperative day, 26 days after cisplatin therapy, he experienced a sudden generalized convulsion followed by lethargy. Neurologic examination showed generalized hyperreflexia and mild weakness in the left lower extremity. He had two additional generalized seizures.

Cranial computed tomography (CT) scans revealed low-density areas, and cranial T2-weighted magnetic resonance (MR) images showed bilateral areas of increased signal intensity in the occipital, parietal, and frontal white matter (Fig 1A and B). Laboratory investigations showed no anemia or neutropenia, although mild hypomagnesemia was noted (1.4 mEq/L; normal, 1.6 to 2.1 mEq/L). Lumbar puncture was normal, with an opening pressure of 135 mm H_2O. MR angiography revealed no abnormal findings; venous sinuses were clearly demonstrated and venous thrombosis was excluded. The patient was treated with intravenous nicardipine hydrochloride, propranolol hydrochloride, glycerol, and phenytoin. Three days later, his blood pressure improved and he regained full consciousness. On the following days he reported visual hallucinations, although these soon resolved, as did the left-sided paresis. He was discharged with no neurologic deficit. Follow-up MR examination 6 months later showed complete resolution of the abnormalities (Fig 1C and D).

Discussion

The frequency of convulsions induced by cisplatin therapy has been estimated at 2.7% to 10% (1–4). Most cases of cisplatin-associated encephalopathy have ensued after dosages of less than 500 mg/m^2, and occurrence does not seem to be dose-dependent (2, 4). Onset has varied from 6 hours to 3 months after the start of treatment (2), and has been reported at varying intervals after cessation of cisplatin therapy. Accumulation of cisplatin in the CNS is thought to induce cytotoxic damage (4), although the precise mechanism is still unknown. Encephalopathy appears to be reversible in most cases (1–4). Usually, no abnormalities are seen on cranial CT or MR studies (1, 2, 4).

Although our patient had several convulsions followed by clouded consciousness 26 days after starting cisplatin therapy, his recovery was complete. Acutely, a neuroradiologic examination showed white matter abnormalities (most likely, edema in the occipital, parietal, and frontal lobes), which disappeared with therapy for hypertension and edema. Clinically, the neuroradiologic abnormalities fulfilled the diagnostic criteria for RPLS, a recently proposed cliniconeuroradiologic category

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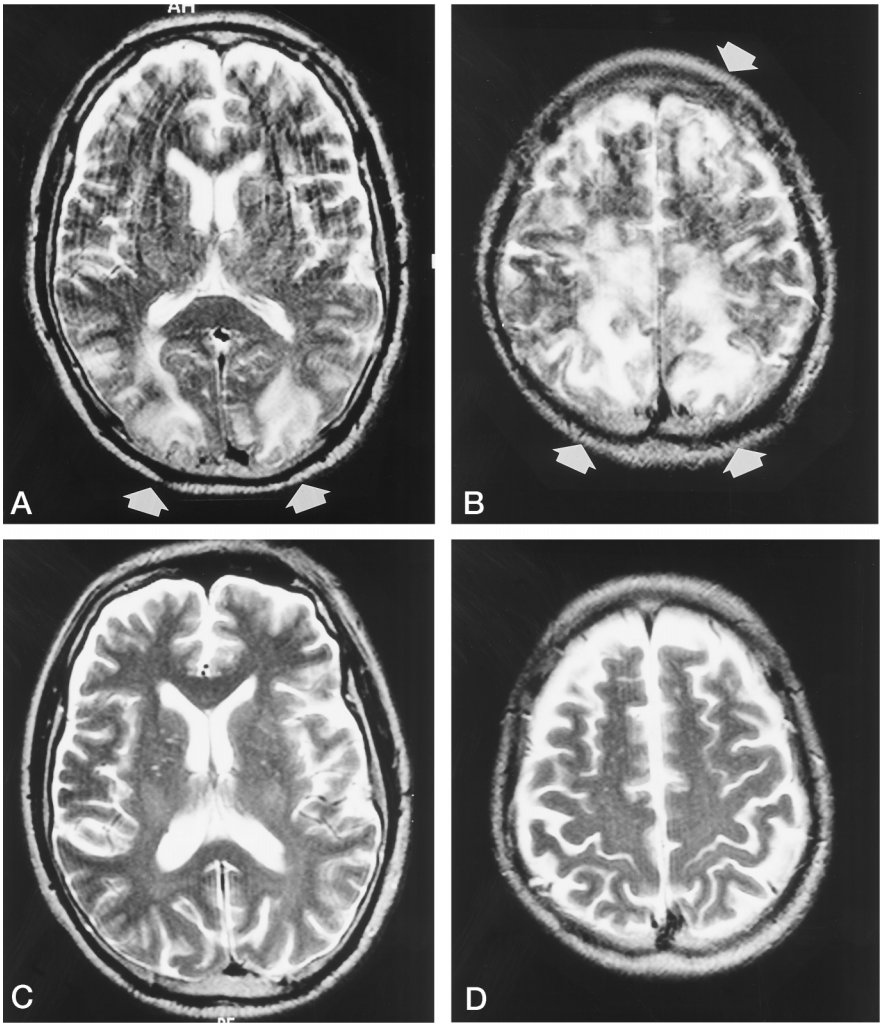

FIG 1. 70-year-old man in whom reversible posterior leukoencephalopathy syndrome developed after chemotherapy with cisplatin and amputation of the left upper limb for osteosarcoma.

A and *B*, T2-weighted MR images (4000/120/1 [repetition time/echo time/excitations]) show bilateral areas of high signal intensity (*arrows*) in the occipital, parietal, and frontal white matter. The motion artifacts were caused by the fact that the patient was actually ill and unable to cooperate for the examination.

C and *D*, T2-weighted MR images (4000/120/1) obtained 6 months later show the high-signal abnormalities have completely disappeared.

characterized by seizures; visual abnormalities, including blurring or cortical blindness; headache, nausea, and vomiting; lethargy or confusion; and hypertension (5). The clinical picture is associated with reversible white matter edema on CT and MR examinations (5). With adequate treatment, all abnormalities resolve in a few weeks. RPLS has been recognized in a wide variety of clinical contexts, including hypertensive encephalopathy, eclampsia, and immunosuppressive treatment for neoplasms or to prevent rejection after organ transplantation. A similar case has been reported in a patient receiving the anticancer drug cytarabine (6).

The precise mechanisms of cerebral edema in RPLS induced by cisplatin is still unknown, but it is considered to be a brain-capillary leak syndrome related to hypertension and fluid extension (5). Systemic hypertension was recognized in our patient. Little has been documented about the relationship between cisplatin-related encephalopathy and hypertension. Cyclosporine is well known to be one of the causative drugs of RPLS (7, 8), and it may induce sympathetic hyperactivity and, as a result, hypertension (9). Furthermore, cyclosporine has a cytotoxic effect on the vascular endothelium, leading to brain-capillary leakage, and acute blood-brain barrier disruption, which may trigger vasogenic edema (5, 10, 11). The mechanism of cyclosporine toxicity may also explain why other drugs induce RPLS.

Hypomagnesemia is occasionally recognized in cisplatin-related encephalopathy, as it was in our case, and represents a suspected exacerbating factor for encephalopathy (1, 4). Considering that magnesium sulfate is often used to prevent convulsions in eclamptic patients (12) and that hypomagnesemia is often seen in patients in whom cyclosporine encephalopathy develops (13), magnesium may be involved in the pathophysiology of RPLS and could be the drug of choice in treating this syndrome.

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Please see the Editorial on page 591 in this issue.