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Reversible posterior leukoencephalopathy syndrome following combinatorial cisplatin and pemetrexed therapy for lung cancer in a normotensive patient: A case report and literature review

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Abstract. Reversible posterior leukoencephalopathy syndrome (RPLS) is a rare neurological syndrome of the brain, causing symptoms such as headaches, seizures, altered mental status and visual disturbances. The condition is predominantly associated with hypertension, eclampsia, renal impairment, cytotoxic drugs, immunosuppressive agents and molecular targeted agents, but the precise underlying mechanism of RPLS is not fully understood. The present study describes the case of a 65-year-old female patient with stage IIA non-small cell lung cancer who received cisplatin/pemetrexed treatment at the Leo W. Jenkins Cancer Center. Following 3 cycles of this therapy, the patient was referred to the Emergency Department of Vidant Medical Center with an altered mental status, subsequently presenting with epileptic seizures, a fever and a headache. A neurological examination revealed generalized hyperreflexia and paraparesis, with extensor posturing of the bilateral lower extremities. The lumbar puncture and electroencephalography results were normal, but cranial computed tomography (CT) scans revealed attenuation abnormalities in the bilateral parietal region and the left occipital lobe, with suspected metastasis. Cranial T2-weighted magnetic resonance imaging (MRI) indicated bilateral regions of increased signal intensity in the occipital, temporal and periventricular white matter. The patient was treated with anticonvulsants, steroids and antihypertensive drugs, recovered gradually from the symptoms and regained full consciousness. However, the patient reported residual weakness, presenting with an Eastern Cooperative Oncology Group score of 3, reflective of an inability to independently perform daily activities and self-care. A brain MRI performed 10 days later demonstrated that the subcortical edema had partially subsided. The patient was discharged on day 15 post-admission. A follow-up cranial CT examination 1 month later indicated a partial resolution of the abnormalities. The present report reviews similar associated cases, and also discusses the clinical features and mechanisms underlying RPLS. Although it is typically reversible, RPLS is a serious and potentially life-threatening adverse condition if left untreated. Early recognition of this condition is crucial for the prompt control of the patient's blood pressure or withdrawal of cytotoxic drugs in order to reverse this syndrome.

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Abbreviations: RPLS, reversible posterior leukoencephalopathy syndrome; NSCLC, non-small cell lung cancer; CT, computed tomography; MRI, magnetic resonance imaging

Key words: reversible posterior leukoencephalopathy syndrome, cisplatin, pemetrexed

Introduction

Reversible posterior leukoencephalopathy syndrome (RPLS) was first described by Hinchey *et al* (1) as an acute illness that causes symptoms such as hypertension, headaches, seizures, altered mental status and visual disturbances, and which is usually reversible following the removal of the causative agents and the control of the patient's blood pressure. RPLS is characterized by white matter edema, particularly involving the bilateral occipital and posterior parietal lobes of the brain (1). Involvement of other areas of the brain, including the frontal lobes, cerebellum, basal ganglia and brain stem, has also been reported.

RPLS is primarily associated with hypertension, eclampsia, renal impairment, cytotoxic drugs, immunosuppressants and molecular targeted agents. The list of common antineoplastic drugs that predispose patients to RPLS is expanding, and includes cisplatin, L-asparaginase, thalidomide, vinflunine, methotrexate, vincristine and cytarabine (2-8). Certain combination regimens have also been associated with RPLS, including a combination treatment of ziv-aflibercept with cisplatin and pemetrexed, the cyclophosphamide, hydroxydaunorubicin, Oncovin and Prednisone

regimen, intrathecal methotrexate and intravenous ifosfamide, idarubicine and etoposide, bevacizumab/folinic acid, fluorouracil and irinotecan, and capecitabine and cyclophosphamide (9-13).

The mechanisms underlying RPLS have been postulated to be either severe hypertension leading to failed auto-regulation and endothelial injury/vasogenic edema, or vasoconstriction leading to brain ischemia and subsequent vasogenic edema. However, the mechanism by which cytotoxic agents cause RPLS in a normotensive environment is not fully understood, but the disruption of the blood-brain barrier is suspected to be a major contributory factor (14).

The present report describes a normotensive patient who had received cisplatin/pemetrexed for treatment of non-small cell lung cancer (NSCLC) and who subsequently developed RPLS, but was able to recover following treatment. Written informed consent was obtained from the patient's family.

Case report

The current report describes the case of a 65-year-old female patient that presented to the Leo W. Jenkins Cancer Center (Greenville, NC, USA) in July 2014 with stage IIA NSCLC [tumor-node-metastasis staging score, T1N1M0 (15)] on the left upper lobe, with an enlarged left hilar lymph node. The patient received cisplatin/pemetrexed (75 and 50 mg/m^2, respectively) by intravenous administration, as neoadjuvant chemotherapy, every 3 weeks. However, 3 days after the third cycle of this therapy, the patient was referred to the Emergency Department of Vidant Medical Center (Greenville, NC, USA)presenting with progressive confusion, followed by tonic-clonic seizures, a fever, abdominal pain and a headache. Neurological examination indicated a limited attention span, disorientation, generalized hyperreflexia and paraparesis with extensor posturing of the bilateral lower extremities and reduced dorsiflexion capability. The blood pressure of the patient was 137/89 mmHg (normal range, 100-140/60-90 mmHg). Biological investigations at admission revealed a normal white blood cell count and platelet count, borderline hyponatremia (134 mmol/l; normal range, 135-145 mmol/l) and mildly elevated ammonia levels (45 mmol/l; normal range, 11-35 mmol/l). Electroencephalography and a lumbar puncture gave normal results, with an opening pressure of 140 mm H_2O, and no organisms were cultured. Cranial computed tomography (CT) scans revealed attenuation abnormalities on the bilateral parietal region and left occipital lobe, with suspected metastasis. Cranial T2-weighted magnetic resonance imaging (MRI) revealed bilateral areas of increased signal intensity in the occipital, temporal and periventricular white matter (Fig. 1A).

The patient experienced multiple generalized seizures following admission, which were resolved by lorazepam treatment (2 mg, every 2 h as required). Anticonvulsants (levetiracetam; 1,500 mg every 12 h), dexamethasone (4 mg, every 6 h) and antihypertensive agents (amlodipine, 5 mg daily; metoprolol, 25 mg twice daily) were then administered as required in order to treat the remaining symptoms. The patient's mental condition gradually recovered and full consciousness was regained, but the patient reported residual weakness with an ECOG score of 3, reflective of poor ability to function with regard to daily activity and self-care. A brain MRI scan performed 10 days later indicated partial alleviation of the subcortical edema (Fig. 1B). The patient was discharged on the day 15 post-admission, and a follow-up cranial CT examination 1 month later demonstrated improved, but not complete, resolution of the abnormalities. The patient succumbed to the disease in September 2014.

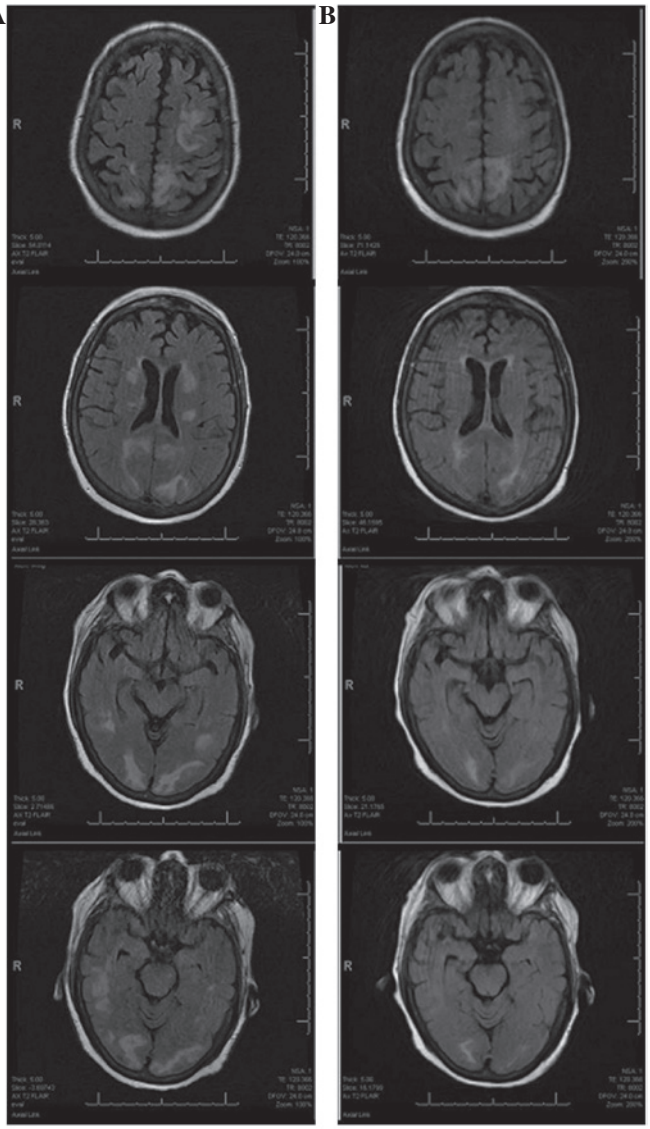

Figure 1. Reversal of diffusion abnormalities in a 65-year-old woman with reversible posterior leukoencephalopathy syndrome associated with cisplatin/pemetrexed treatment. T2-weighted magnetic resonance imaging indicated bilateral regions of increased signal intensity in the occipital, temporal and periventricular white matter (A) upon admission and (B) during the follow-up examination 10 days later, following supportive and symptomatic therapy.

Discussion

The present study was unable to confirm whether cisplatin or pemetrexed was responsible for the onset of RPLS, but there are multiple previous studies of cisplatin-associated RPLS, whether alone or in combinatorial treatments alongside other cytotoxic drugs (5,16-23). However, to the best of

Table I. Characteristics of reported cases of patients with cancer with cisplatin-associated RPLS.

First author (ref.)	Age, years/ gender	Diagnosis	Drug treatment	Cycle	Time after chemotherapy	Clinical presentation	Highest BP, mmHg	Location of lesions from CT/MRI data	Recovery time
Ito *et al* (5)	70/M	Osteo-sarcoma	DDP, 50 mg, injected intraarterially	1st	26 days	Generalized convulsions; lethargy; hyperreflexia; mild weakness in lower left extremities; hallucination at later stages; mild hypomagnesemia	180/100	Bilateral occipital lobes; white matter of the parietal and frontal lobes	Symptoms subsided after 3 days; CR confirmed by MRI in 6 months
Dersch *et al* (16)	41/F	NSCLC	DDP, gemcitabine, bevacizumab	7th	4 weeks	Focal seizures; headaches; ataxia; hallucinations	245/140	Bilateral frontal and parietal cortical/subcortical regions, right thalamus; right temporal cortical/subcortical regions	Symptoms subsided following a reduction in BP. PR confirmed by MRI in 5 weeks
Zahir *et al* (17)	23/M	Germ cell tumor	DDP, 20 mg/m^2; etoposide 100 mg/m^2, (days 1-5)	1st	A few hours	Tonic-clonic seizures; blurring of vision; hyperreflexia of the lower limbs	170/110	Bilateral periventricular, posterior parietal and occipital regions	Symptoms subsided in 48 h. Repeated DDP administration without dose reduction; no neurological complications occurred
Kwon *et al* (18)	58/F	Gallbladder cancer	Gemcitabine, 1,200 mg/m^2, days 1 and 8; DDP, 60 mg/m^2, days 1-5	3rd	2 weeks	Headache; dizziness; tonic-clonic seizures	170/90	Patchy cortical/subcortical lesions on occipital and parietal lobes	CR confirmed by MRI after 10 days
Maeda *et al* (19)	50/M	Bladder cancer	Gemcitabine, 1,200 mg/m^2, days 1 and 8; DDP, 60 mg/m^2, days 1-5	2nd	5 weeks	Semicomatose; hypercalcemia	Almost normal	Subcortical lesions on the posterior occipital lobes and thalamus	Symptoms improved after a few days; PR confirmed by MRI in 4 weeks. Succumbed to respiratory failure 6 weeks after RPLS treatment
Rangi *et al* (20)	49/F	Gestational trophoblastic disease	Etoposide and DDP for 2 months, then gemcitabine, carboplatin and Taxol for 2 months	4th	2 months	Headache; confusion; tonic-clonic seizures; bilateral visual disturbance	Normal	Subcortical white matter of the posterior cerebellar hemispheres and occipital and parietal lobes	Symptoms subsided in 48 h. CR confirmed by MRI in 6 weeks
Onujiogu *et al* (21)	64/F	Fallopian tube cancer	Paclitaxel, 135 mg/m^2; DDP, 100 mg/m^2, injected intraperitoneally	1st	5 days	Lethargy; aphasia; leucopenia; hyponatremia	160/93 with hypertension history	White matter throughout the frontal, parietal, occipital and temporal lobes	Symptoms subsided in 4 days. Almost CR confirmed by MRI after 12 days

Table I. Continued.

First author (ref.)	Age, years/ gender	Diagnosis	Drug treatment	Cycle	Time after chemotherapy	Clinical presentation	Highest BP, mmHg	Location of lesions from CT/MRI data	Recovery time
Paul *et al* (22)	37/n/a	Gastric cancer	DDP, 50 mg/m^2 and 5-fluorouracil, 2,000 mg/m^2	1st	During chemotherapy	Tonic-clonic seizures	U	White matter of the parietal and occipital lobes	Multiple recurrences
Nomura *et al* (23)	61/F	Ovarian carcinoma	DDP and etoposide	2nd	Following second course	Headache; fever; partial seizure; confusion; mild right hemiparesis; cortical blindness after 10 days	U	Subcortical white matter of the occipital cortex; gracile fasciculus; dorsal root ganglia	Symptoms subsided after 1 month. Succumbed to aspiration pneumonia on the 43rd day following treatment
Present study	65/F	NSCLC	DDP, 75 mg/m^2 and pemetrexed, 50 mg/m^2	3rd	3 days	Altered mental status; generalized seizures; fever; headache; hyperreflexia; paraparesis of the lower extremities	Almost normal	White matter of the occipital, temporal and periventricular regions	Symptoms subsided after 10 days. PR confirmed by MRI after 10 days

RPLS, reversible posterior leukoencephalopathy syndrome; BP, blood pressure; CT/MRI, computed tomography/magnetic resonance imaging; n/a, not available; NSCLC, non-small cell lung carcinoma; DDP, cisplatin; U, unknown; CR, complete resolution; PR, partial resolution.

our knowledge, no studies have indicated that pemetrexed alone can induce RPLS; it is therefore conceivable that cisplatin is predominantly responsible for the RPLS reported in the present study.

RPLS is a rare neurological syndrome of the brain that was first defined by Hinchey *et al* in 1996 (1). The condition is reported in numerous patients with eclampsia, acute hypertensive encephalopathy associated with renal disease and those receiving immunosuppressive therapy or interferon. An association with cisplatin administration in cancer patients has been widely reported in previous studies (Table I) (5,16-23), predominantly occurring within the first 3 cycles of chemotherapy, with the exception of one late-onset case in the 7th cycle (16). In the majority of cases, patients develop hypertension, and additionally present with headaches, seizures, altered mental status and visual disturbances, whilst normotension is only observed in a few cases (5,16-18). Cranial CT/MRI usually indicates cortical/subcortical edema in the bilateral occipital and parietal lobes; uncommon areas in which to observe legions include the thalamus, the cerebellum, the periventricular regions, and the frontal and temporal lobes. Symptoms typically improve rapidly upon gaining control of the patient's blood pressure, upon treatment with anticonvulsants and/or upon withdrawal of cytotoxic drugs. It is notable that this syndrome has serious and potentially life-threatening adverse effects if left untreated.

The precise pathophysiology of RPLS is incompletely understood. As hypertension presents in the majority of patients with RPLS, hypertensive encephalopathy is a probable mechanism of its development. Sudden elevations in systemic blood pressure disrupt the blood-brain barrier, causing the local exchange of fluids. The cerebral white matter is composed of myelinated fiber tracts in an extracellular matrix containing glial cells, arterioles and capillaries, and is susceptible to vasogenic edema (1). The carotid vessels are supplied with a greater number of sympathetic adrenergic innervations than those of the vertebral-basilar system; this inherent deficiency of sympathetic adrenergic innervation may inhibit the vasoconstriction of posterior cerebral vessels, making them prone to RPLS development (24). In normotensive patients with RPLS, including the present case, another possible hypothesis is that damage to the endothelial cells of cerebral vessels by cytotoxic drugs destroys the blood-brain barrier, as proposed in a rat model (14). Numerous RPLS patients have demonstrated metabolic abnormalities, including fever, leukocytosis, hyponatremia, hypocalcemia and hypomagnesemia (2-8), implying that metabolic abnormalities may disturb the integrity of the blood-brain barrier and lead to cerebral edema. In a previous study, a postmortem examination of a patient with cisplatin-associated RPLS indicated severe nerve cell loss, gliosis and spongy changes to the bilateral occipital cortex, including the visual field; furthermore, mild to moderate demyelination in the subcortical white matter of the occipital cortex, gracile fasciculus and dorsal root ganglia was observed. Notably, platinum was detected in the bilateral occipital cortex, spinal cord and cauda equina, suggesting that platinum may contribute to the damaging effects of RPLS (23).

The use of an intravenous cisplatin/pemetrexed regimen can be associated with RPLS; although typically reversible, this syndrome is serious and can be fatal if left untreated. Early recognition is vital in order to control the blood pressure or to withdraw cytotoxic drugs in a timely manner for the

reversal of RPLS. The precise underlying mechanism of RPLS is not fully understood and is posited to be multifactorial, but it is likely to be associated with the integrity of the blood-brain barrier.

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