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Case report

Cisplatin-induced non-convulsive encephalopathy

Olga Lyass, Alexander Lossos, Ayala Hubert, Maya Gips and Tamar Peretz
Department of Oncology, Hadassah University Hospital and Hebrew University–Hadassah Medical School, POB 12000, Jerusalem 91120, Israel. Tel: (+972) 2 6776725; Fax: (+972) 2 6427485.

Cisplatin is a widely used chemotherapeutic agent implicated in a range of adverse effects affecting the nervous system. Among the others, convulsive encephalopathy is rare and its pathogenesis is unknown. We report an 84-year-old woman with adenocarcinoma of the ovary who developed two fully reversible episodes of non-convulsive encephalopathy, each following a course of cisplatin-based chemotherapy and thus confirming a causal relationship to the agent. The patient presented 7 and 10 days after treatment with acute confusional state, a partial left homonymous hemianopia and a left extinction hemihypesthesia. Brain MRI showed old-standing cerebral microvascular changes and EEG revealed right parieto-occipital periodic lateralized epileptiform discharges over a generalized background activity slowing. This case adds further to the clinical diversity of cisplatin toxicity and, in view of the similarity to a recently defined disorder of posterior leukoencephalopathy, suggests regional endovascular injury rather than a direct cerebral toxicity as the initial event in the evolution of encephalopathy. [© 1998 Rapid Science Ltd.]

Key words: Adverse effect, cisplatin, encephalopathy.

Introduction

Cisplatin is a heavy metal complex containing a central atom of platinum surrounded by two chloride and two ammonia atoms in the *cis*-position of the horizontal plane.[1] The anticancer activity of the drug is related to the inhibition of DNA synthesis by causing inter- and intra-strand cross-linking, and the major clinical indications for cisplatin application include testicular, ovarian, bladder, lung and aerodigestive tract malignancies.[1]

One of the most potent chemotherapeutic agents, cisplatin is also one of the most toxic. Adverse effects of the agent include nausea and vomiting, nephrotoxicity and electrolyte imbalance, myelosuppression, anaphylactic-like reactions, and ocular and vascular toxicity.[2] Neurotoxicity is the main dose-limiting side effect of cisplatin affecting preferentially the peripheral nervous system. Most patients develop a predominantly sensory polyneuropathy, sensory-neural hearing loss and Lhermitte's sign,[3] whereas transient convulsive encephalopathy (Table 1), cerebral vascular events[1,2] and low pressure hydrocephalus[5] are less common.

We describe a patient with recurrent ovarian carcinoma who developed two fully reversible episodes of non-convulsive encephalopathy, each following a course of cisplatin-based chemotherapy and thus confirming a causal relationship to the agent.

Case report

An 84-year-old woman was admitted with acute confusional state which developed 1 week after the second chemotherapy course with cisplatin (80 mg/m^2 as a 48 h continuous i.v. infusion, preinfusion antiemetic being ondansetron 8 mg i.v.) and cyclophosphamide (CTX; 800 mg/m^2) given for a recurrent ovarian cancer. Three years previously, evaluation of a pelvic mass revealed a papillary serous adenocarcinoma of ovary stage III-C. Debulking surgery and treatment with cisplatin and CTX led to a pathological complete response documented on a second-look laparotomy. This was followed by a consolidation chemotherapy with cisplatin, methotrexate and 5-fluorouracil. Two years after the initial diagnosis, she developed a local abdominal recurrence and was retreated with cisplatin and CTX discontinued in anticipation of renal toxicity, and changed to paclitaxel and later to leucovorin/ 5-fluorouracil with hexamethylmelamine. However, an increase in tumor mass necessitated reintroduction of cisplatin (160 mg/m^2 total cumulative dose) and CTX.

On initial examination, she was afebrile and there were no signs of cardiorespiratory compromise. Neurologically, she was somnolent at rest but agitated and disorientated when aroused. She could not

Correspondence to O Lyass

Table 1. Characteristics of patients with cisplatin-induced encephalopathy[a]

Age/sex[b]	Diagnosis	Treatment[c]	Interval	Main neurologic manifestations		Duration	Residual deficit	Rechallenge	Reference
				Encephalopathy	Seizures				
30/M	NSGCTT	cisplatin (NR), VBL, Bleo	4 h	cortical blindness	generalized	3 days	no	no	4
23–66/3M, 5F	NSGCTT, GCTO, ovarian carcinoma	cisplatin (NR), ADM, CTX, VBL, Bleo	7 h–4 months	1 dysphasia, 3 hemiparesis	focal and generalized	NR	no	3 patients	5
22/M	NSGCTT	cisplatin (500), VBL, Bleo	7 days	confusion, tunnel vision	generalized	17 days	no	no	6
13/F	GCTO	cisplatin (200), VBL, Bleo	11 days	no	focal	1 hour	no	yes	7
26/M	NSGCTT	cisplatin (300), VBL, Bleo	13 days	aphasia	generalized	2 days	no	yes	7
61/F	ovarian carcinoma	cisplatin (325), VP-16	10 days	confusion, hemiparesis, cortical blindness	focal	1 month	no	no	8
32/M	NSGCTT	cisplatin (500), VBL, Bleo	6 days	cortical blindness	no	5 days	no	no	7
32/M	testicular seminoma	cisplatin (700), VBL	10 days	aphasia, homonymous hemianopia	no	2 days	no	no	7
36/F	carcinoma of cervix	cisplatin (200)	13 days	cortical blindness	no	6 days	no	no	9
62/F	Fallopian tube carcinoma	cisplatin (500), ADM	several hours	confusion, cortical blindness, headache	no	weeks	yes	no	10
36/M	NSGCTT	cisplatin (300), VBL, Bleo	7 days	confusion, homonymous hemianopia, extinction hemihypesthesia, headache	no	5 days	yes	no	11
84/F	ovarian carcinoma	cisplatin (860), CTX	7 days	confusion, homonymous hemianopia, extinction hemihypesthesia	no	10 days	no	yes	present

[a] M, male; F, female; NSGCTT, non-seminomatous germ cell tumor of testis; GCTO, germ cell tumor of ovary; VBL, vinblastine; Bleo, bleomycin; ADM, adriamycin; CTX, cyclophosphamide; VP-16, etoposide, NR, not reported.
[b] Age in years at diagnosis of encephalopathy.
[c] Total cumulative dose of cisplatin is specified in parentheses in mg/m^2 where available.

concentrate on simple memory or motor tasks and was easily distracted by the surroundings. There was no neck rigidity, dysphasia or motor deficit, and her eye movements, pupillary light reflexes and fundi were normal. A bedside examination of the visual fields disclosed a partial left homonymous deficit and sensation testing showed a left extinction hemihypesthesia.

Brain MRI demonstrated a mild diffuse atrophy and multiple non-enhencing foci of hyperintensity on T2 and PD-weighted images involving the periventricular white matter and pons, and accompanied by a moderate loss of white matter substance. The findings were consistent with old-standing microvascular changes. Lumbar puncture was slightly traumatic; the cerebrospinal fluid (CSF) was under normal pressure, and contained 500×10^6/l erythrocytes, 10×10^6/l polymorphonuclear leukocytes, 0.89 g/l of protein (normal 0.2–0.65 g/l) and normal glucose levels. Cytology, cultures for bacteria and fungi, and assay for cryptococcal antigen were negative; serologic tests for varicella-zoster virus, herpes simplex virus, Epstein–Barr virus and cytomegalovirus showed no evidence of active infection. EEG showed complex repetitive discharges occurring at 2.5 s intervals over the right parieto-occipital area, and composed of spiky and slow-wave elements consistent with the diagnosis of periodic lateralized epileptiform discharges (PLED) accompanied by a generalized slowing of background activity.

Peripheral blood count revealed a mild anemia of 6.8 mmol/l hemoglobin and leukocytosis of 20×10^9/l with 83% granulocytes related to the granulocyte colony-stimulating factor (G-CSF) support given in anticipation of leukopenia; platelet count and coagulation profile were normal. Blood chemistry showed sodium of 132 mmol/l (normal 135–145), glucose of 11.1 mmol/l (normal 3.9–5.6), magnesium of 0.6 mmol/l (normal 0.8–1.3); calcium, potassium, creatinine, blood urea nitrogen, albumin, ammonia and thyroid functions were normal. Blood and urine cultures yielded negative results. Chest X-ray, electrocardiogram, echocardiogram and carotid arteries doppler study were unremarkable.

Empiric therapy with ceftriaxone, ampicillin and acyclovir was initiated to treat a possible menigoencephalitis; phenytoin, thiamine and magnesium sulfate were added, G-CSF was withdrawn, and the patient received fluid and electrolyte support. Over 10 days, her condition gradually improved, she became oriented, cooperative and fully ambulant. The visual field and sensory deficit disappeared parallel to normalization of the EEG, the white blood cell count returned to normal, and the treatment with antibiotics and acyclovir was discontinued in face of the relevant laboratory results.

Two weeks following the admission, she was discharged with a presumptive diagnosis of cisplatin-induced encephalopathy and the chemotherapy regimen was changed to include carboplatin (pre-infusion antiemetic is ondansetron 8 mg i.v.) with CTX given unsuccessfully for two courses. In view of the prior response to cisplatin-based treatment and after obtaining informed consent, we reintroduced cisplatin 4 months after the initial event. It was given at the original schedule but without G-CSF. Ten days later, the patient developed a similar episode of acute confusional state. Blood chemistry was unremarkable, there was no leukocytosis, EEG showed identical PLED activity over the right hemisphere and repeat brain MRI was unchanged. Phenytoin blood level was subtherapeutic, and she was treated with i.v. diazepam and phenytoin with complete neurological recovery in a few days. The patient died 2 years later due to end-stage ovarian cancer.

Discussion

The patient described in this report developed an acute, afebrile, non-convulsive encephalopathy that was temporally related to the administration of cisplatin-based chemotherapy and resolved without leaving any neurological deficit. The causal relationship to the agent in this case is further supported by the exclusion of various metabolic, cardiovascular or infectious causes, metastatic involvement, and by a retreatment offered on clinical judgment.[13] Of the other concurrent medications, G-CSF may be associated with a similar reaction,[14] but it was only used during the first of the two episodes. Absence of a similar reaction to carboplatin only supports its low neurotoxic potential.

Encephalopathy represents the central nervous system (CNS) toxicity of cisplatin. Since its initial description in 1980,[4] at least 17 additional patients have been reported (Table 1) with an observed frequency of 0.2–2.7% per treatment courses.[5,7] It typically starts within 2 weeks after the treatment with generalized or, less often, focal tonic-clonic seizures accompanied by acute or subacute confusional state, central visual problems and headache. Our patient presented with signs of global confusional state and central visual disturbance but without seizures—a combination characteristic of a less common, non-convulsive encephalopathy (Table 1). In either case, the symptomatology

resolves without leaving any residual neurological deficit even after repeat episodes.[5,7]

The diagnosis of cisplatin-induced encephalopathy requires exclusion of other potential causes of encephalopathy in cancer patients and no pathognomonic laboratory abnormality is described. In all cases studied, computed brain tomography is normal[4-11] and CSF analysis shows only non-specific changes, such as elevated protein level,[7,11] high opening pressure[11] and occasionally a few crenated red blood cells.[4] EEG is usually abnormal, and demonstrates electrophysiological evidence of cortical dysfunction manifested by generalized or focal slow-wave activity[4-7,10] and epileptiform discharges.[9] Similarly, laboratory evaluation in our patient was unremarkable, but EEG findings consistent with PLED have not been previously reported in this clinical set-up. This pattern is mostly seen in acute or subacute unilateral cerebral lesions, such as stroke, tumor, abscess and encephalitis.[15] Rarely, it may also occur in association with chronic lesions when exposed to toxic or metabolic disorder,[15] and we suspect that prior microvascular changes revealed on the brain MRI in our patient may have predisposed her to the observed reaction.

The pathogenesis of cisplatin-associated encephalopathy remains unknown at present and may be manifold. Fever, neutropenia, thrombocytopenia, hypomagnesemia, renal dysfunction, hypokalemia and hyponatremia are considered by some to contribute to the CNS toxicity of cisplatin,[4-11] but, as in our patient, these are mostly mild and are not invariably present. Some of these factors, as well as high peak levels or prolonged exposure to cisplatin, may probably lower the seizure threshold but are usually not severe enough to account for encephalopathy.[5] As in our patient, the disorder characteristically develops after several courses of cisplatin with a total dose ranging between 200 and 700 mg/m^2. The relatively high cumulative dose and a detectable cisplatin level in pathologically affected brain tissue[4] and CSF[4] in a few examined cases suggest the possibility of a toxic effect related to cisplatin accumulation in the CNS.[7] However, the lack of a clear dose-effect relationship[5] and the ready reversibility of encephalopathy in most cases argue against. Furthermore, since the CNS seems to be effectively protected from cisplatin by an intact blood-brain barrier,[16] initial events must first alter its integrity to enable cisplatin penetration.

Neurological findings in the present and in other cases of cisplatin-associated encephalopathy, as well as the single autopsy report,[8] indicate a conspicuous involvement of the occipital and parietal regions of the brain. Clinically, this is revealed by homonymous hemianopia, cortical blindness and extinction hemihypesthesia (Table 1), all of which evolve on a background of global cerebral dysfunction. The EEG abnormalities in our patient confirm this regional predilection. Similarly, predominantly posterior encephalopathy is also seen in eclampsia, hypertensive encephalopathy, renal insufficiency and with immunosuppressive therapy,[17] but the cause of such a selective regional vulnerability is unknown. In these conditions, extensive but reversible cerebral edema, represented on the MRI as posterior leukoencephalopathy, is probably induced by a dysregulation of the local microvasculature or a direct endothelial toxicity that damages the blood-brain barrier.[17] Since cisplatin is also implicated in vascular toxicity,[6,12] a similar mechanism may underlie the development of cisplatin-associated encephalopathy. We did not identify posterior leukoencephalopathy in our patient; however, this imaging finding is not invariable,[14] but rather represents one extent of the clinical spectrum. On the other hand, old-standing cerebral microvasculopathy observed on her MRI may have contributed to the initial cisplatin-induced vascular damage culminating in encephalopathy.

The management of cisplatin-induced encephalopathy is based on supportive measures, anticonvulsants, avoidance of CNS depressants, and on the correction of a possible fluid, electrolyte and pH imbalances. We and others[5,7] have not regarded only encephalopathy as a contraindication to further therapy with cisplatin, although this decision must be taken individually in conjunction with other clinical factors. In addition, awareness that such an encephalopathy is transient and reversible should be reassuring to both the patient and the physician.

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