Carboplatin-Paclitaxel chemotherapy and general anaesthesia in an ovarian cancer patient: a combination to provoke reversible posterior leukoencephalopathy syndrome?

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Reversible posterior leukoencephalopathy syndrome is a syndrome of heterogeneous aetiology characterised by typical clinical and radiological findings. The occurrence of reversible posterior leukoencephalopathy syndrome in cancer patients is rapidly increasing. So when a cancer patient suddenly experiences symptoms of altered consciousness, convulsions, headache and/or visual disturbances, reversible posterior leukoencephalopathy syndrome should always be included in the differential diagnosis. In this paper, we describe a case of a patient who developed reversible posterior leukoencephalopathy syndrome after receiving a regimen with carboplatin and paclitaxel.

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Introduction

Reversible posterior leukoencephalopathy syndrome (RPLS) is a syndrome of heterogeneous aetiology characterised by typical clinical and radiological findings. We report a case of this rare disease in a patient with an ovarian carcinoma treated with carboplatin and paclitaxel chemotherapy.

Case report

A 67-year old woman without relevant medical history presented with symptoms of abdominal pain and was diagnosed with a high grade serous ovarian adenocarcinoma with diffuse abdominal metastases (FIGO stIIIC). The treatment, with curative intent, started with induction carboplatin (AUC 5 mg/ml*min) and paclitaxel (175 mg/m2) in a three-weekly schedule. A favourable response was observed after the fourth cycle: a decrease of CA125 (from 480 U/ml to 17.2 U/ml, reference <30 U/ml), an improvement of the clinical symptoms, regression of the ovarian tumour mass, and normalisation of the peritoneal and omental metastasis.

A debulking surgery was performed three weeks after the fourth cycle. Postoperatively the patient recovered quickly. During the first 48h, there was an impaired diuresis with discretely increased creatinine levels. Twenty mg furosemide was given twice with prompt recovery of the renal function. No abnormalities of the electrolytes were observed.

A few days after the surgical procedure, the patient suddenly complained of neck pain, blurred vision and dizziness. Control of parameters could not reveal any

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abnormalities. Shortly afterwards, the patient experienced contractions in the face, severe headache and a bilateral loss of vision. Her blood pressure remained well controlled, with mean arterial pressure around 90mmHg. Neither clinical nor ophthalmological examination, nor a brain computed tomography (CT) could reveal any abnormalities. The blood test showed no significant deviations. On ECG, no abnormalities were seen. In the acute phase she was transferred to the midcare department for more intensive follow-up. Both acetylsalicylic acid and valproic acid were administered at that time.

Because of the unexplained blindness with suspected cerebral origin, a magnetic resonance imaging (MRI) scan of the brain was performed. On the axial fat-suppressed FLAIR-weighted image, hyperintense subcortical oedema can be seen in both occipital lobes (*Figure 1*). This image was highly suggestive for reversible posterior leukoencephalopathy syndrome. The patient was monitored continuously: her respiratory and hemodynamic status remained stable, she had a preserved diuresis and she remained afebrile. The symptoms of the patient gradually diminished over the first 24h. After three days all symptoms had disappeared, except the complaints of diplopia. During the following days, she had a relatively elevated blood pressure (MAP round 110 mmHg) and amlodipine 5 mg was started as a treatment. In order to prevent further cerebral oedema, methylprednisolone was given for several days.

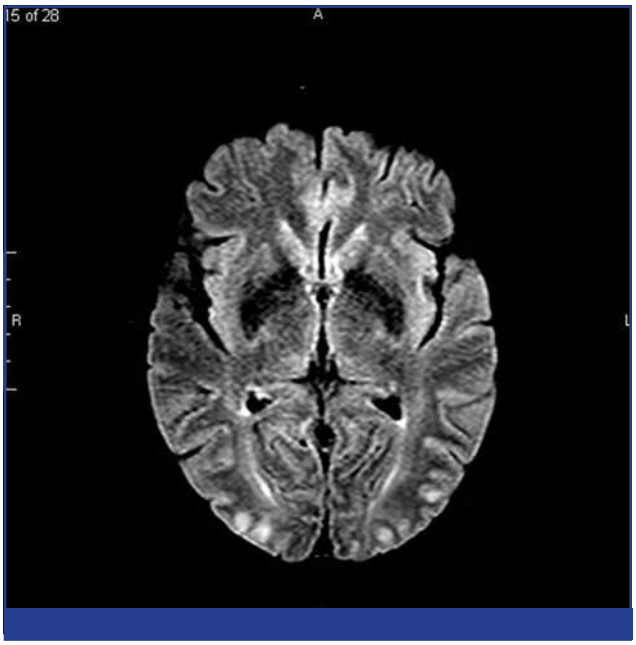

Figure 1. On this axial fat-suppressed FLAIR-weighted image, hyperintense subcortical oedema is seen in both occipital lobes.

Six weeks later the oncologic treatment for the ovarian carcinoma was restarted with two cycles of paclitaxel-only treatment.

Discussion

Reversible posterior leukoencephalopathy syndrome (RPLS) is a syndrome of heterogeneous aetiology characterised by typical clinical and radiological findings. RPLS was described for the first time in a case series report in 1996 by Hinchey et al.[1]

The pathogenesis of RPLS remains poorly understood. The key mechanism is thought to be related to failure of vascular cerebral autoregulation. Under normal circumstances, the intracerebral blood flow is regulated by dilatation and/or constriction of the sympathetic innervated vessels, which may protect against the fluctuations in systemic perfusion pressure. A disturbed autoregulation can lead to secondary lysis of the blood with extravasation of fluid and protein into the extravascular space. This leakage is detected on neuroimaging studies as vasogenic oedema. Endothelial dysfunction by immunosuppressive and cytotoxic agents could also play a role in the pathophysiology. The toxicity on the vascular endothelium can lead to capillary leakage, which may lead to vasogenic oedema.[1-4] In a recent study, Fitzgerald et al. report a statistical significant elevation of serum lactate dehydrogenase (LDH), a marker of endothelial dysfunction, at the onset of RPLS toxicity in cancer patients receiving chemotherapy. This supports the hypothesis that endothelial damage is a factor, if not the primary event, in the pathophysiology of RPLS.[5] In this patient, no increase in LDH was observed.

Several medical conditions as well as specific treatment modalities have been suggested as causes of RPLS. The most common are hypertensive encephalopathy, eclampsia, renal failure, cytotoxic agents and immunosuppressive agents (*Table 1*). RPLS also occurs in patients under immunosuppressive treatment, up to three months after exposure to the triggering factor.[6]

The occurrence of RPLS in cancer patients is rapidly increasing. This is due to the increasing complexity of cancer treatment, the more frequent use of targeted therapy, the side effects of these drugs and other associated medical conditions.[8] RPLS is not necessarily caused by toxic doses and previous exposure does not protect against the harmful product.[4-9]

Table 1. Medical conditions at risk for RPLS.[3,7]

Chemotherapy	Platinum analogues (cisplatin, carboplatin, oxaliplatin) Antimetabolites (gemcitabine) Folate antagonists Anthracyclines Vinca alkaloids
Targeted Therapy	Bevacizumab, rituximab, sorafenib, sunitinib, bortezomib, RAF kinase inhibitor, ipilimumab, thalidomide
Other Drugs	dexamethasone, G-CSF, interferon, linezolid, azathioprine
Immunosuppressive therapy	cyclosporine, tacrolimus, methotrexate
Auto-immune diseases	Systemic lupus erythematosus, Systemic sclerosis, Rheumatoid arthritis, Polyarteritis nodosa, Wegener granulomatosis, Antiphospholipid syndrome, Cryoglobulinemia
Other medical conditions	Hypertension, Blood transfusion, Eclampsia, Hypercalcemia, Hypomagnesemia, Haemolytic uremic syndrome, Transplantation, Contrast media exposure (cerebral, coronary angiography), Pheochromocytoma, Primary aldosteronism, Acute or chronic renal failure, Thrombotic Thrombocytopenic purpura, Bone marrow transplant

In literature, there are multiple reports of RPLS associated with platinum analogues, especially with cisplatin, and only a few cases are reported with carboplatin.[3,4,10] The association of paclitaxel with RPLS was far less reported in the literature. Furthermore, in all of these cases, the paclitaxel was associated with a platinum analogue, so that the question arises whether it was effectively paclitaxel or more likely the platinum analogue that was responsible for the onset of RPLS.[3,11] As far as we know this is the second case described in the literature of RPLS after a combined treatment of carboplatin and paclitaxel.[3] However it is not certain that RPLS in this case can be attributed to chemotherapy. In literature, the temporal relationship between onset of RPLS and treatment with cytotoxic agents is not clear, and the only evidence available is from single case reports and small series. In our case, the interval was one month which makes it possible, according to the evidence, for other chemotherapeuticals.[5] Rangi et al. described a case in which there was a striking temporal relationship between the occurrence of RPLS after general anaesthesia with chemotherapy in the recent history. They suggest a possible delayed interaction between cytotoxic drugs and anaesthesia: pre-sensitisation of the patient with a cytotoxic agent and precipitation of RPLS by the exposure to the anaesthetics. This is of course an assumption, for which additional research is needed.[12] Study of the literature could not reveal other case reports suggesting a possible link between anaesthetics and RPLS. In addition, our patient had not experienced similar problems after previous general anaesthesia. In our case, no other medication had been administered that could have provoked RPLS according to the literature.[3,7]

The most common clinical manifestations of RPLS are headaches, disturbance of consciousness, altered mental functioning, seizures, visual abnormalities and vomiting. The onset of these clinical signs is mostly subacute and often begin with seizures.[1,3,4] Blood pressure is elevated in a number of cases, but it is not a consistent finding.[1,6] The seizures mostly start focally and then evolve to generalised tonic clonic seizures. Single seizures are rare. They are usually followed by successive convulsions and even a status epilepticus.[13] Most of the patients present with changes of behaviour and alertness: lethargy and somnolence, temporarily alternated with agitation. In exceptional cases, stupor and coma may occur.[1] Visual problems such as visual loss, blurred vision, visual hallucinations and hemianopsia are often associated, which suggest occipital lobe origin. In clinical trials no abnormalities of the pupillary reflexes or fundoscopy have been found.[14] There are neither diagnostic criteria nor specific clinical signs, which complicate the diagnosis of RPLS.[3,6] There is an extensive differential diagnosis that includes numerous diseases with similar clinical and radiographic signs.[6,8] Especially in cases with an acute onset, the distinction can be difficult. Because of the need for a treatment for hypertension, it is important to distinguish between RPLS and ischemic stroke.[6]

Key messages for clinical practice

1. RPLS is a syndrome of heterogeneous etiology characterised by typical clinical and radiological findings.
2. The occurrence of RPLS in cancer patients is rapidly increasing.
3. RPLS should always be included in the differential diagnosis when a patient reports with altered consciousness, convulsions, headache and/or visual disturbances.

The clinical signs are associated with changes of the white matter, indicative for vasogenic oedema, mostly in the posterior parietal–temporal–occipital regions of the brain.[1] Despite the name, RPLS is rarely isolated in the posterior parieto-occipital area, but is also found in the frontal lobes, basal ganglia and brainstem.[3] Neuroimaging is essential and can be performed by CT, but MRI remains the gold standard for diagnosis.[8] The anatomic extent of the vasogenic oedema on the MRI scan correlates with the outcome of the patient.[9] Diffusion weighted imaging can be used to distinguish RPLS from ischemic infarction.

There are no guidelines for the treatment of RPLS because of the various presentations and the limited clinical reports. The most important element in the treatment of RPLS is to determine the possible cause.[6] Supportive management and discontinuation of causative medications are the mainstays of treatment. Supportive therapy includes blood pressure control and prevention of brain oedema with corticosteroids, which might speed up recovery.[3]

The prognosis of RPLS is favourable in most cases. The clinical course is usually reversible within a period of days to weeks, if the disease is recognised and treated in time.[8] Without proper management, neurological signs and other symptoms can persist.[6]

When a cancer patient suddenly experiences symptoms of altered consciousness, convulsions, headache and/or visual disturbances, RPLS should always be included in the differential diagnosis. In this way, early treatment can be started and prolonged neurological symptoms avoided.[8]

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