Sudden cortical blindness following cisplatin: a case of reversible posterior leukoencephalopathy syndrome

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Key words Reversible posterior leukoencephalopathy syndrome, anti-angiogenesis, cisplatinum, magnetic resonance imaging

Summary

Sudden blindness, headache, nausea and vomiting developed seven days after a retreatment with cisplatin monochemotherapy in a patient suffering from a relapsed epithelial ovarian carcinoma. The clinical and radiological findings corresponded to the reversible posterior leukoencephalopathy syndrome (RPLS), a rare and dramatic disorder, which in the majority of cases is fully reversible. The pathogenesis of RPLS still needs to be defined, however, insufficiency of the autoregulatory capability of the brain vasculature and disruption of the blood-brain barrier seem to play an important role.

(BJMO 2008;vol 2;1:32-5)

Introduction

Major clinical symptoms leading to the tentative diagnosis of reversible posterior leukoencephalopathy syndrome (RPLS) are headache, seizures, and an acute and bilateral visual impairment, often combined with accelerated arterial hypertension. In recent years, this entity has become increasingly recognized by the term RPL syndrome, which was first used by *Hinchey et al.* in 1996[1]. Causes and associations include hypertensive encephalopathy, eclampsia, thrombotic thrombocytopenic purpura (TTP)/ hemolytic-uremic syndrome (HUS), coagulation disorders such as the antiphospholipid syndrome, connective tissue diseases, and certain drugs (mainly cytotoxic and immunosuppressive agents).[2,3,4] In addition to the medical history and the leading clinical symptoms, there are characteristic radiological findings in magnetic resonance imaging (MRI), the imaging modality of choice.

Patient history

A 62-year old woman with a history of an epithelial cystadenocarcinoma of the left ovary FIGO Stage IIIc, initially treated with primary optimal debulking surgery (< 1 cm residual tumour) followed by six cycles of adjuvant chemotherapy (cisplatin 75 mg/sqm and paclitaxel 175 mg/sqm), suffered from a locoregional relapse five years after diagnosis. The initial chemotherapy resulted in episodes of prolonged (> 7 days) grade IV thrombocytopenia. She suffered from both chronic grade II sensory and motor neuropathy and three years after initial diagnosis she developed a progressive and worsening anaemia. Bone marrow examination showed this to be caused by an alkylator type of myelodysplastic syndrome (MDS).

After 4 cycles of chemotherapy with pegylated liposomal doxorubicin, an attempt at surgical resection was not successful because of invasion into the bony pelvic wall. External beam radiotherapy to a total dose of 45 Gy was administered. Six months later she experienced exacerbating gluteal pains, which were rapidly increasing in severity. Computed Tomography (CT) scans revealed progression of the pelvic recurrence. Because of the invalidating pain, the previous impossibility of local resection and the rapid progression after radiotherapy, cisplatin monochemotherapy (75 mg/sqm) was initiated in spite of earlier poor haematological tolerance and chronic neurotoxicity.

Acute toxicity of cisplatin therapy was acceptable, however on the seventh day after the first administration, she developed a sudden bilateral visual loss,

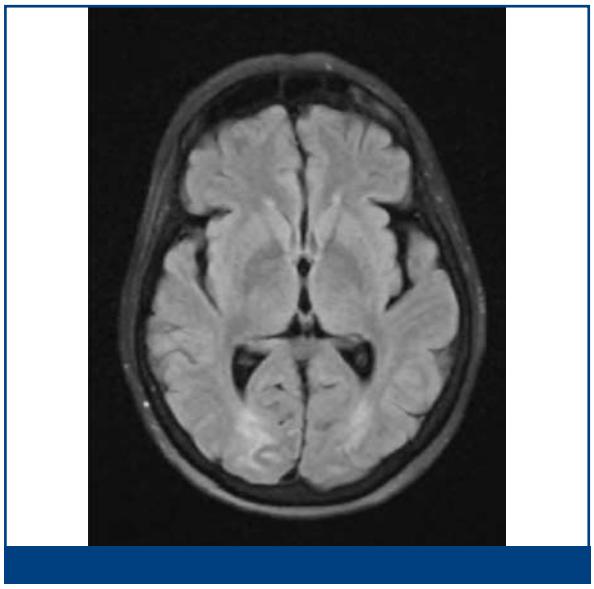

Figure 1. Magnetic resonance imaging of the brain 3 days after sudden visual loss. Presence of occipital cortical and subcortical hyperintensity on FLAIR images can be observed.

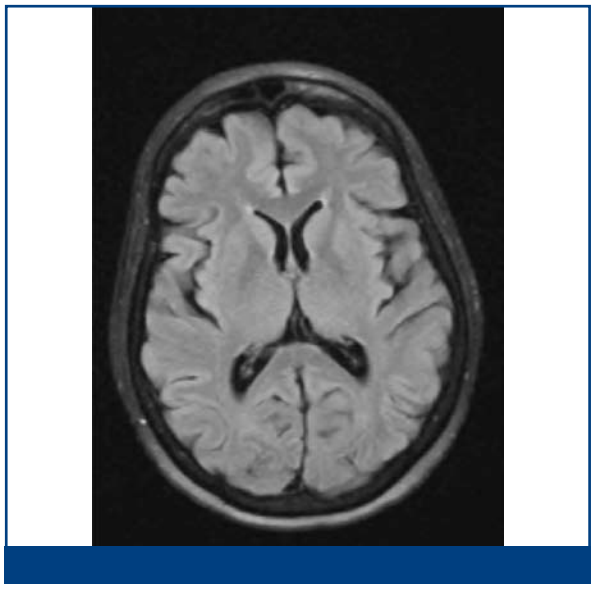

Figure 2. Follow-up magnetic resonance imaging two months later showed almost complete resolution of hyperintensity on FLAIR images.

with visual acuity dropping to minimal perception of light in both eyes, severe headaches, nausea and vomiting. Paradoxically, she initially seemed to be rather unaware of her visual disability (Anton syndrome).[1] Blood pressure (143/75 mmHg) and Glasgow coma scale (15/15) remained normal. Ophtalmological and neurological examination showed no other abnormalities. An urgent CT scan (without intravenous contrast) proved normal. Laboratory investigations showed a moderate thrombopenia (52,000/mm^3), minimal hypomagnesemia (1.4mg/dL) and hypokalemia (3.2 meq/L). The patient was treated empirically with intravenous corticosteroids and over the next 48 hours there was a gradual and near-complete recuperation of vision. Magnetic resonance imaging 3 days after sudden visual loss revealed occipital cortical and subcortical hyperintensity on FLAIR (fluid-attenuated inversion recovery) images, with a slightly decreased apparent diffusion coefficient (ADC) (*Figure 1*).

A follow-up MRI 2 months later showed almost complete resolution of the hyperintensity on FLAIR images (*Figure 2*).

Discussion and conclusions

RPLS is a rare syndrome characterised by seizures, acute visual abnormalities, including cortical blindness, headache, nausea and vomiting, lethargy and confusion, which is often associated with hypertension.[1] It has been described in patients with acute hypertensive encephalopathy, eclampsia or in patients receiving immunosuppressive therapy or chemotherapy. The onset and resolution of cortical blindness observed in our patient correlated with the radiographic abnormalities and were consistent with the natural history of RPLS. The focal nature and immediate onset of our patient's visual disturbance might suggest an ischemic event. However, imaging studies pointed to vasogenic edema as the chief cause, rather than infarction. Furthermore, the patient's clinical improvement correlated with radiographic occipital lobe edema resolution.

Toxic damage to the vascular endothelium or blood-brain barrier caused by immunosuppressant and cytotoxic medications is postulated to contribute to the pathophysiological features of RPLS. Direct causal relationships between chemotherapy agents and RPLS have been difficult to establish, and the correlation is more common with cyclosporine and tacrolimus. Other associated agents include methotrexate, the alpha interferons, granulocyte-colony stimulating factor, erythropoietin, cisplatinum, carboplatinum, cytarabine, cyclophosphamide, doxorubicin and vincristin.[2-8]

Several other investigators observed an association between RPLS and bevacizumab (Avastin®) administration.[9,10] Other case reports mention similar events in patients treated with either sunitinib (Sutent®) or sorafenib (Nexavar®) suggesting that this probably

Key messages for clinical practice

1. RPLS can complicate a wide variety of medical disorders.
2. Clinical features include headache, nausea and vomiting, and cortical blindness.
3. It is a sudden, dramatic event, sometimes associated with denial of the visual loss.
4. Hypertensive encephalopathy, eclampsia, certain cytotoxic and immunosuppressive agents are the most common causes.
5. Different agents interfering with the VEGFR2 pathway are also known to cause this syndrome. These anti-VEGF agents might well become the most common cause of RPLS in the oncology clinic.
6. MRI scanning is the diagnostic procedure of choice.
7. Prompt reduction of blood pressure if increased and correction of even minor electrolyte disbalance (Magnesium) are advocated, in combination with withdrawal of the putative agent.
8. The syndrome is in general reversible with recovery in days.

is a class effect of anti-VEGF agents.[11,12]

The most frequent finding in neuro-imaging studies is bilateral edema (although some asymmetry can be observed) in general only involving the white matter in the parieto-occipital regions. These abnormalities tend to improve or resolve completely on follow-up imaging. Although some irreversible cases have been reported, mostly clinical signs are completely reversible. Hypointense T1 lesions and hyperintense T2 lesions are often seen bilaterally in occipital and parietal lobe white matter.

The mechanism of RPLS in patients remains to be fully determined. However, in analogy with the pathogenesis in hypertensive encephalopathy and eclampsia, insufficiency of the autoregulatory capability of brain vasculature and disruption of the blood-brain barrier seem to play an important role. A direct cytotoxic effect produced by certain drugs, might be the cause of vascular endothelial damage, leading to endothelial dysfunction. This results in vasospasms, reduced tissue perfusion, activation of the coagulation cascade and extravasation of fluid. A relative paucity of sympathetic adrenergic innervation to the vertebral-basilar system is suggested to account for the tendency in this syndrome to involve structures supplied by the posterior circulation. In the RPL after bevacizumab administration, vasospasms may be a result of an altered signalling through the vascular endothelial growth factor-receptor (VEGFR) pathway leading to a decreased amount of nitric oxid and vasospasms. Hypomagnesemia has been noted in association with RPLS after cisplatin chemotherapy and might also be implicated in the pathogenesis of pre-eclampsia. Cisplatin has been shown to cause both acute and chronic vascular damage, including Raynaud's phenomenon, hypertension and cerebrovascular disease.[13] Various pathophysiologic conditions may contribute to these complications including thrombosis secondary to vascular endothelial injury or thromboembolic events. Cisplatin-associated encephalopathy mostly arises after doses of less than 500 mg/sqm and the occurrence does not seem to be dose-related. Onset of symptoms varies from 6 hours to 3 months after initiation of treatment and at varying intervals after cessation of cisplatin therapy.

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Conflicts of interest: none reported.

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