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Central Retinal Artery Occlusion during Cisplatin and Etoposide Chemotherapy for Small Cell Lung Cancer

Case Report

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Abstract

We present our findings in a case of central retinal artery occlusion (CRAO) that developed in a patient while being treated with intravenous cisplatin (CDDP) and etoposide (VP16) for small cell lung cancer. The patient was a 67-year-old woman who had lung lobectomy for small cell lung cancer. She began adjuvant chemotherapy with CDDP and VP16 after the surgery, and after 13 days of chemotherapy, she developed a sudden painless decrease of vision in her left eye. She was referred to Department of Ophthalmology, and our examination found that her decimal visual acuities were 1.0 OD and light perception OS. Fluorescein angiography showed a CRAO in her left eye. Two months later, she had a sharp pain in the left eye because of neovascular glaucoma, and cyclophotocoagulation was immediately performed. Although her visual function did not recover completely (light perception OS), the pain was alleviated after the cyclophotocoagulation. Physical examinations showed no additional abnormalities of the cardiovascular system. Although a CRAO during chemotherapy is extremely rare, ophthalmologists and internists should remember that a CRAO can develop in patients undergoing combined chemotherapy even though other cardiovascular events may not be present.

Keywords: Central Retinal Artery Occlusion; Cancer; Chemotherapy.

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Introduction

A central retinal artery occlusion (CRAO) is considered to be an acute stroke of the eye that results in profound visual reduction. The majority of CRAOs are caused by platelet fibrin thrombi and emboli that develop in individuals with atherosclerotic disease [1-2]. The risk factors for CRAO include arterial hypertension, diabetes mellitus, carotid artery disease, cerebral vascular accidents, and tobacco smoking. Other risk factors that contribute to CRAO are proatherogenic states, hyperhomocystenemia, factor V Leiden, protein C and S and anti-thrombin deficiencies, anti-phospholipid antibodies, and sickle cell disease [1]. In addition, patients with cancer who receive chemotherapy are at risk for vascular complications such as veno-occlusive disease, venous thrombosis, and vascular ischemia [3]. Pharmacological agents are also considered to be the independent risk factors for vascular events because some, such as platinum based compounds, vinca alkaloids, bleomycin, and tamoxifen, have been shown to cause vaso-occlusive complications. However, retinal vascular occlusions in patients with cancer who receive chemotherapy is a rare complication and has not been frequently reported.

We describe a case of CRAO that developed in a cancer patient while undergoing intravenous cisplatin (CDDP) and etoposide (VP16) chemotherapy.

Case Report

A 67-year-old woman with stage IIIA small cell lung cancer underwent left lung lobectomy 2 months before first our examination. She began adjuvant chemotherapy with intravenous CDDP and VP16 after the surgery. After 13 days of chemotherapy, she noted a sudden painless loss of vision in the left eye on awakening. She was referred to our Ophthalmology Department.

Her medical history showed that she had systemic hypertension and diabetes mellitus which were well-controlled. She had smoked for forty years. On her first examination, her visual acuity was

20/20 in the right eye and no light perception in the left eye. The left eye had a relative afferent pupillary defect. Slit-lamp examination and the intraocular pressure (IOP) were normal. Ophthalmoscopy of the left eye showed cloudy swelling of the nerve fiber layer throughout the posterior pole, a cherry-red spot in the macula, and attenuated retinal arteries (Figure1). The right fundus was normal. A diagnosis of left central retinal artery occlusion was made.

We performed eyeball massage, paracentesis, and oral administration of prostaglandin. However, there was no recovery of visual function. Optical coherence tomographic (OCT) images showed an increase in the reflectivity and thickness of the inner retina and a corresponding decrease of reflectivity in the outer layer of the retina of the left eye (Figure2). Fluorescein angiography showed markedly delayed filling of the retinal arteries and increased arterio-venous transit time (Figure3). An echocardiogram and carotid artery ultrasound showed no evidence of a thrombus. The electrocardiogram was normal without arterial fibrillation. Coagulation markers such as the platelet count, prothrombin time, and activated partial thrombin time were within normal limits. Diffusion-weighted magnetic resonance imaging of the head and magnetic resonance angiography (MRA) showed no abnormalities.

Two months later, she had a sharp pain in her left eye which we diagnosed to be caused by neovascular glaucoma (NVG). The IOP in her left eye was increased to 58mmHg (Figure4), and cyclophotocoagulation was immediately performed. Although her visual function did not recover completely (light perception OS), the pain was alleviated after the cyclophotocoagulation. After six months, her vision was no light perception.

Figure 1. Fundus photographs at the initial examination. (A).The right eye is normal. (B). The left eye has retinal edema, a macular cherry-red spot, and attenuated retinal arteries (yellow arrows) indicating a central retinal artery occlusion (CRAO).

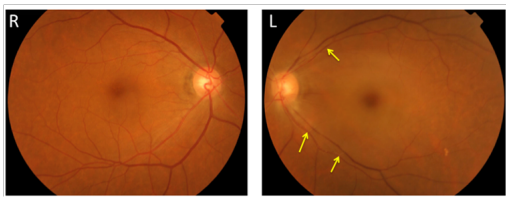


Figure 2. Optical coherence tomographic (OCT) image. The image of the left eye shows increased reflectivity and thickness of the inner retina. The image of the right eye shows a normal retina.

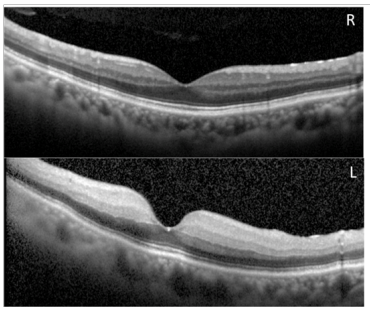


Figure 3. Fluorescein angiograms taken 30 hours after vision loss in the left eye. (A). Right eye. The filling time and pattern are normal. (B). Left eye. The filling time of the retinal arteries is markedly delayed.

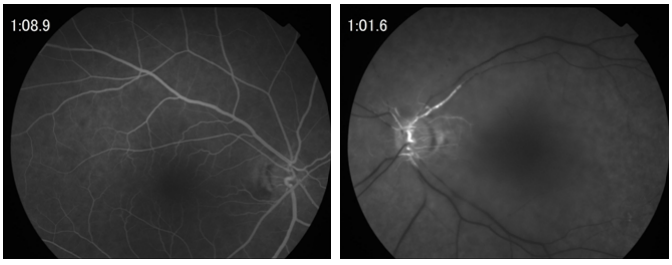
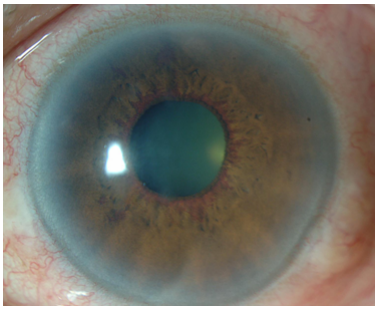


Figure 4. Slit-lamp examination showed mild corneal edema and iris neovascularization at the pupillary margin.



Discussion

Chemotherapy has been associated with the development of several vascular alterations in patients with cancer. This is probably because chemotherapeutic drugs can damage the vascular endothelium, cause a disequilibrium between procoagulant and anticoagulant molecules, induce tumor/endothelial apoptosis, activate cytokines, and increased tissue factor activity [4]. Although a recent systematic review and meta-analysis indicated that there was no significant increase in arterial thromboembolic events associated with CDDP [5], CDDP has been frequently associated with other adverse vascular events [6-10]. The vascular complications associated with CDDP include Raynaud's phenomenon, cardiac ischemia, arterial thrombosis, and ischemic cerebrovascular events [7-9]. A previous study reported that arterial thrombosis was detected in 2.6% of patients receiving CDDP chemotherapy [10]. However, a retinal artery occlusion associated with CDDP is extremely rare. To the best of our knowledge, only two cases of retinal artery occlusion following CDDP chemotherapy have been reported [11, 12]. Both cases did not have any known risk factors for atherosclerosis such as smoking history, hypertension, or diabetes mellitus. Because one of the two cases had a recovery of visual function after the discontinuation of CDDP chemotherapy, the authors suspected an involvement of CDDP in the retinal artery occlusion.

In our case, the patient had several vascular risk factors, however there were no clinical signs of systemic atherosclerosis. This suggested that CDDP probably contributed to the vascular events in some way.

The mechanism of how CDDP chemotherapy causes retinal arterial occlusion was not determined. However, several studies have reported that CDDP can induce platelet activation and elevate the von Willebrand factor, which can cause endothelial injury and potentiate arterial thrombosis [13]. Furthermore, hypomagnesaemia and autonomic dysfunction cause vasospasm [8, 11]. A histological examination of the blood vessels after intravenous CDDP showed vascular intimal edema and detachment with pyknosis of the endothelial cells and thrombus formation [8]. Other ophthalmic complications associated with CDDP chemotherapy include pigmentary maculopathy, altered color perception attributable to cone dysfunction, retinal ischemia with neovascularization, optic neuropathy, and cortical blindness [14-18].

The rate of NVG after CRAO is likely around 15%, which we would not count as rare [19, 20]. The CRAO most likely contributed to the NVG because the MRA findings did not show severe stenosis of the internal carotid artery that would cause the ocular ischemic syndrome. In addition, there was no evidence of ischemic retinopathy caused by diabetic retinopathy because the contralateral eye had no non-perfusion areas caused by diabetic retinopathy. We assume that the retina was not completely ischemic and the metabolism of the inner retina was partially maintained. This would then induce angiogenic factors such as vascular endothelial growth factor which could cause the NVG.

Conclusion

In conclusion, the development of a CRAO in a patient undergoing chemotherapy with intravenous CDDP for small cell lung cancer indicates that clinicians should advise patients to immediately consult an ophthalmologist if they have a sudden decrease in their vision.

Acknowledgements and Declarations

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