• Letter to the Editor •

Fluorescein angiography findings in both eyes of a unilateral retinoblastoma case during intra-arterial chemotherapy with melphalan

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Received: 2018-11-01 Accepted: 2019-04-09

DOI:10.18240/ijo.2019.12.24

Citation: Ozgonul C, Chaudhary N, Hutchinson R, Archer SM, Demirci H. Fluorescein angiography findings in both eyes of a unilateral retinoblastoma case during intra-arterial chemotherapy with melphalan. *Int J Ophthalmol* 2019;12(12):1987-1989

Dear Editor,

Intra-arterial chemotherapy (IAC) is a treatment for retinoblastoma that involves direct injection of chemotherapeutic agent into the ophthalmic artery. The main advantage of this method is the ability to deliver high drug concentration in the tumor with low systemic toxicity[1-2]. However, it has the potential to cause vascular-related ocular side effects of vitreous hemorrhage, branch retinal artery obstruction, ophthalmic artery spasm with reperfusion or obstruction, and choroidal ischemia[3]. To further understand the underlying mechanisms of these vascular side effects, we report the fluorescein angiography (FA) findings of the treated and untreated eyes in a unilateral retinoblastoma patient during IAC with melphalan. A 13-month-old boy was referred with leukocoria in his left eye. Informed consent form was signed by patient's mother. Fundus examination of the left eye showed a retinoblastoma with surrounding localized vitreous seeds, measuring 16×6×9 mm^3, in the macula (Figure 1A). Fundus examination of the right eye was normal.

IAC was performed by the neuro-interventional radiology team under general anesthesia. A Magic 1.5 Fr BALT microcatheter was inserted into the left femoral artery, advanced into the internal carotid and up to the origin of the ophthalmic artery. Once the catheter tip position was confirmed at the origin of the ophthalmic artery by fluoroscopy, 5 mg melphalan was infused in a pulsatile fashion over 30min. There was no anatomical variant of orbital vascular structure. During the 2nd IAC, following the infusion of melphalan, sodium fluorescein dye at a dose of 7.7 mg/kg was injected through the same microcatheter. Real-time FA was recorded by using the RetCam III (Clarity Medical Systems, Pleasanton, California). FA was repeated 4wk later during the 3rd IAC in the same manner, before infusion of the chemotherapy. In both sessions, there was no catheterization or injection of contrast material into the untreated carotid and ophthalmic artery. During both procedures, vital signs and pulmonary compliance values were within the normal range.

We evaluated the FA of both eyes after the 2nd and before the 3rd cycles of IAC. In the first FA, following IAC, the early phase showed delayed choroidal perfusion in the treated left eye. Diffuse retinal arterial narrowing, hypoperfusion of the tumor and less leakage of intra-tumoral vessels were observed in the mid and late phases compared to the second FA before IAC (Figure 1B-1G). Similarly, the FA of the untreated right eye revealed diffuse retinal arterial narrowing and diffuse choroidal hypoperfusion (Figure 2). There was no vascular occlusion. Overall, the brightness of the first FA following IAC was dim compared to the second FA before IAC.

In a non-human primate model, Wilson *et al*[4] reported local vascular complications of IAC with melphalan including retinal artery narrowing, retinal edema, retinal artery precipitates and choroidal hypoperfusion. Moreover, in a study that evaluated FA findings after IAC by Bianciotto *et al*[5], the authors concluded that vascular perfusion of the retina and the choroid can be compromised after IAC. The retinal abnormalities that they found were similar to those seen by Wilson *et al*[4], including ophthalmic artery obstruction in 4% of cases, choroidal perfusion abnormalities in 25%, central and branch retinal artery obstruction in 4% and 13% of cases, respectively. However, these studies did not describe untreated fellow eyes. In our case, the untreated fellow eye demonstrated

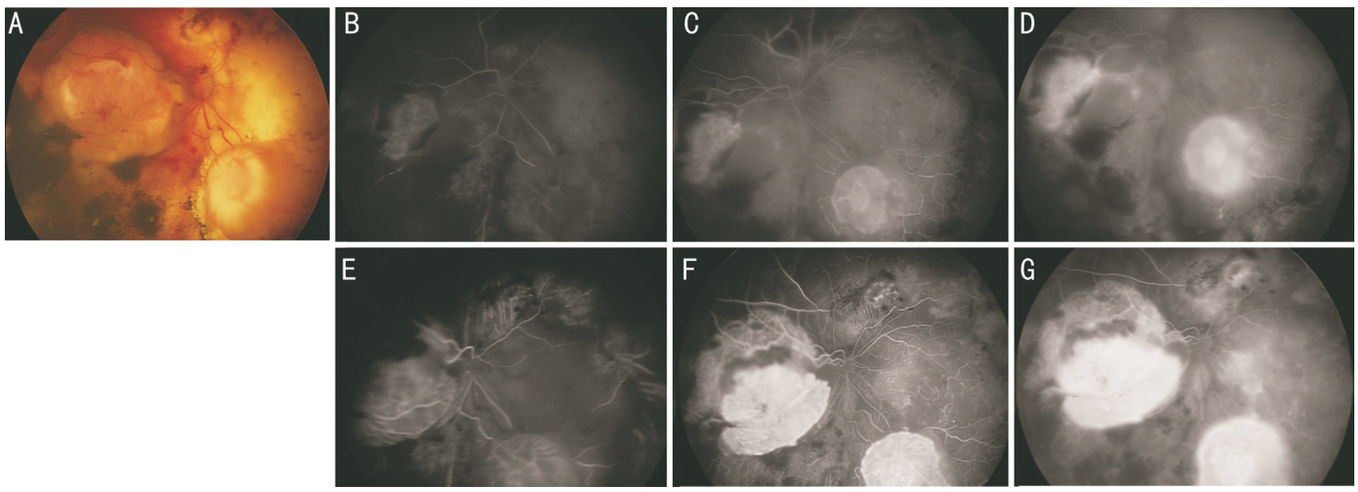

Figure 1 Treated left eye A: Color fundus image. B-D: Early and late phases of the first FA following the 2nd cycle of IAC. Choroidal hypoperfusion in the early phases, diffuse retinal arterial narrowing, and hypoperfusion of the tumor are visible. E-G: Early and late phases of the second FA before the 3rd cycle of IAC.

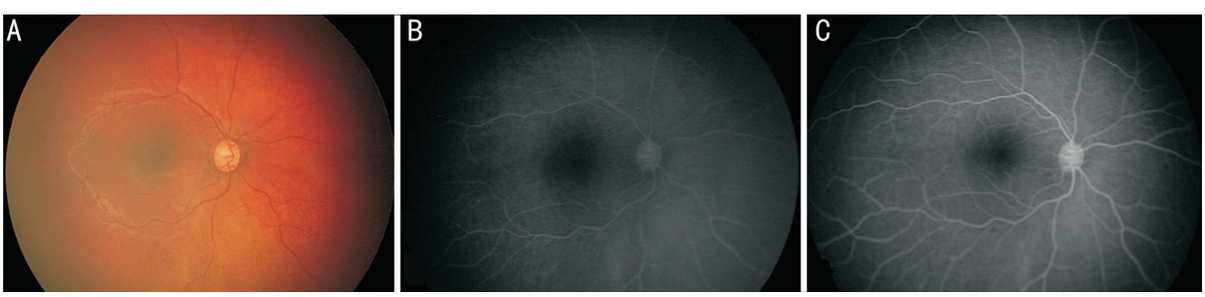

Figure 2 Untreated right eye A: Color fundus image. B: Late phase of the first FA following the 2rd cycle of IAC. Diffuse retinal arterial narrowing and diffuse hypoperfusion of choroid are noted. C: Late phase of the 2rd FA before the 3rd cycle of IAC.

FA findings similar to the treated eye. Vasoconstriction of retinal vessels was observed in both eyes.

To our knowledge, this is the first case report to demonstrate evidence of vascular changes in the untreated fellow eye of a unilateral retinoblastoma patient. Vascular complications following IAC have been proposed to be due to the catheter-related vascular insult, endothelial cell toxicity of melphalan or foreign body embolization[6]. In an animal model, Steinle *et al*[7] showed that melphalan caused endothelial cell inflammation and leukostasis of the ophthalmic artery following 3 IAC with melphalan. Kato *et al*[8] demonstrated that 29% of patients experienced a severe pulmonary compliance event during IAC by analyzing peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP), tidal volume (TV), oxygen saturation (SpO_2), and end tidal CO_2 ($EtCO_2$). The decrease in pulmonary compliance values might play a role in vascular changes during IAC. However, in our case, pulmonary compliance values were within normal limits. Our finding of vascular spasm in the untreated fellow eye might suggest that vascular spasm might occur in both treated and untreated eyes during the IAC despite the normal pulmonary compliance and multiple factors might play role in the etiology.

ACKNOWLEDGEMENTS

Conflicts of Interest: Ozgonul C, None; **Chaudhary N,** None; **Hutchinson R,** None; **Archer SM,** None; **Demirci H,** None.

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