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LETTER TO THE EDITOR

Cystoid macular edema following intravitreal chemotherapy treatment for retinoblastoma

To the Editor:

Vitreous disease either at presentation or relapse is a poor prognostic factor for eye survival in retinoblastoma.[1]

We report two cases of cystoid macular edema (CME) confirmed on optical coherence tomography (OCT) scans following intravitreal chemotherapy (IVC) with melphalan, an adverse effect not previously reported.

A 1-year-old male child with bilateral retinoblastoma (advanced group D OD, group E OS) underwent enucleation of the left eye and six cycles of carboplatin, etoposide, and vincristine (CEV) systemic chemotherapy, focal therapy, and two cycles of intraarterial chemotherapy (IAC) with melphalan to the right eye.

Six months later, his right eye developed vitreous relapse, and received three weekly doses of 30 μg intravitreal melphalan. Three weeks after the final treatment, the visual acuity dropped from 20/32 to 20/125 measured with preferential looking tests (Cardiff Acuity Cards) despite satisfactory tumor control. Macular OCT showed presence of CME (Figure 1A). Treatment with oral prednisolone improved visual acuity to 20/50, with resolution of CME (Figure 1B). Two months later, the CME recurred, responding to topical nonsteroidal anti-inflammatory drugs (NSAID). At 2-year follow up, visual acuity was stable at 20/40.

A 2-year-old female child with bilateral retinoblastoma (group C OD, group E OS) underwent left eye enucleation, six cycles of systemic

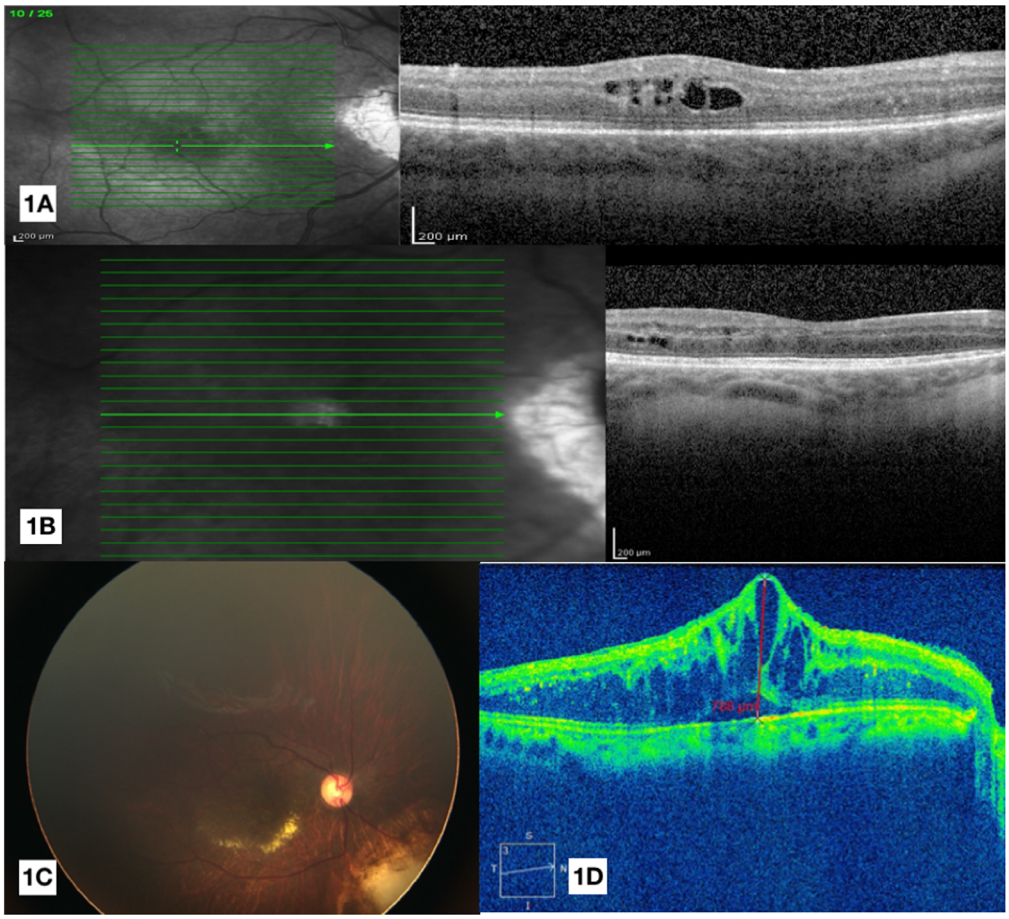

FIGURE 1 A, Optical coherence tomography (OCT) scan showing macular edema following intravitreal chemotherapy (IVC). B, Near complete resolution following treatment. C, Fundus photo with drusen-like macular deposits after IVC. D, OCT scan showing cystic macular edema with increased macular thickness of 768 μm

CEV chemotherapy, and focal therapy for the right eye. Two years later, a localized vitreous recurrence responded partially to Iodine-125 brachytherapy. She received three weekly injections of 20 μg melphalan with good response. One month after the last injection, she developed CME, confirmed with OCT scan (Figure 1C and D). She was treated with topical NSAID, oral acetazolamide, and sub-Tenon triamcinolone injection. The macular edema resolved over 6 months. Visual acuity remained unchanged before and after IVC at 20/400.

IVC has been used to control persistent or recurrent vitreous seeding in patients with retinoblastoma refractory to systemic chemotherapy and/or IAC.[2] Although melphalan was the first drug to be used for IVC, it is now common to use two agents (topotecan with melphalan). Several centers have reported excellent results with single- and dual-agent chemotherapy.[1,3-6]

The reported adverse effects of IVC melphalan include salt and pepper pigmentary retinopathy, diffuse hemorrhagic retinopathy, vitreous hemorrhage, hypotony, cataract, pupil posterior synechiae, iris depigmentation, iris recession, filtering conjunctival bleb formation, and focal scleromalacia. No cases of cystoid macular edema have been reported.[7–11]

Sterile saline is used to prepare melphalan, and it is unlikely that this vehicle agent provides retinal toxicity.[12]

Dose-dependent retinal toxicity has been described in animal models using electroretinograms (ERGs) and histological evaluation. Increasing doses of melphalan reduced the amplitude of flash ERG a and b waves and resulted in scar tissue formation in the outer retinal layers.[13] This has been confirmed in humans with Francis et al reporting a 5.3 μV reduction in ERG amplitude seen on a 30 Hz photopic flicker with each intravitreal dose. Concomitant use of IAC in patients with darkly pigmented eyes was a significant risk factor for increased amplitude loss.[7,14] The retinopathy is abrupt, permanent, and non-progressive once treatment is stopped.[7] Other studies have reported greater reduction in amplitudes on 30 Hz photopic flicker ERGs at 17.7 μV[2] and 30 μV.[7] However, Ghassemi et al reported no change with the a or b waves on bright-flash ERG following treatment, highlighting that the mass response of the retina may not highlight specific macular pathology.[5]

OCT-proven damage following treatment with melphalan includes inner and outer retinal atrophy, choroidal atrophy, and a loss of foveal depression.[15] With the increased availability of portable and intraoperative OCT devices, we suspect that subclinical damage may be more apparent in the retina, especially within the macula. Visual acuity in children can be difficult to reliably obtain, and objective measurements with 30 Hz flicker ERG and OCT may therefore become necessary.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Berry JL, Shah S, Kim F, Jubran R, Kim JW. Integrated treatment during the intravitreal melphalan era: concurrent intravitreal melphalan and systemic chemoreduction. *Ocul Oncol Pathol*. 2018;4(6):335-340.
2. Abramson DH, Ji X, Francis JH, Catalanotti F, Brodie SE, Habib L. Intravitreal chemotherapy in retinoblastoma: expanded use beyond intravitreal seeds. *Br J Ophthalmol*. 2019;103(4):488-493.
3. Brodie SE, Munier FL, Francis JH, Marr B, Gobin YP, Abramson DH. Persistence of retinal function after intravitreal melphalan injection for retinoblastoma. *Doc Ophthalmol*. 2013;126(1):79-84.
4. Munier FL, Soliman S, Moulin AP, Gaillard M-C, Balmer A, Beck-Popovic M. Profiling safety of intravitreal injections for retinoblastoma using an anti-reflux procedure and sterilisation of the needle track. *Br J Ophthalmol*. 2012;96(8):1084-1087.
5. Ghassemi F, Shields CL, Ghadimi H, Khodabandeh A, Roohipoor R. Combined intravitreal melphalan and topotecan for refractory or recurrent vitreous seeding from retinoblastoma. *JAMA Ophthalmol*. 2014;132(8):936-941.
6. Rao R, Honavar SG, Sharma V, Reddy VAP. Intravitreal topotecan in the management of refractory and recurrent vitreous seeds in retinoblastoma. *Br J Ophthalmol*. 2018;102(4):490-495.
7. Francis JH, Schaiquevich P, Buitrago E, et al. Local and systemic toxicity of intravitreal melphalan for vitreous seeding in retinoblastoma: a preclinical and clinical study. *Ophthalmology*. 2014;121(9):1810-1817.
8. Ji X, Hua P, Li J, Li J, Zhao J, Zhao P. Intravitreal melphalan for vitreous seeds: initial experience in China. *J Ophthalmol*. 2016;2016:4387286.
9. Francis JH, Marr BP, Brodie SE, Abramson DH. Anterior ocular toxicity of intravitreous melphalan for retinoblastoma. *JAMA Ophthalmol*. 2015;133(12):1459-1463.
10. Ghassemi F, Shields CL. Intravitreal melphalan for refractory or recurrent vitreous seeding from retinoblastoma. *Arch Ophthalmol*. 2012;130(10):1268-1271.
11. Smith SJ, Smith BD, Mohney BG. Ocular side effects following intravitreal injection therapy for retinoblastoma: a systematic review. *Br J Ophthalmol*. 2014;98(3):292-297.
12. Buitrago E, Lagomarsino E, Mato G, Schaiquevich P. Stability of melphalan solution for intravitreal injection for retinoblastoma. *JAMA Ophthalmol*. 2014;132(11):1372-1373.
13. Shimoda Y, Hamano R, Ishihara K, et al. Effects of intraocular irrigation with melphalan on rabbit retinas during vitrectomy. *Graefes Arch Clin Exp Ophthalmol*. 2008;246(4):501-508.
14. Francis JH, Brodie SE, Marr B, Zabor EC, Mondesire-Crump I, Abramson DH. Efficacy and toxicity of intravitreous chemotherapy for retinoblastoma: four-year experience. *Ophthalmology*. 2017;124(4):488-495.
15. Aziz HA, Kim JW, Munier FL, Berry JL. Acute hemorrhagic retinopathy following intravitreal melphalan injection for retinoblastoma: a report of two cases and technical modifications to enhance the prevention of retinal toxicity. *Ocul Oncol Pathol*. 2017;3(1):34-40.