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Macular toxicity of vital dye after pars plana vitrectomy for idiopathic epiretinal membrane: A case report

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ABSTRACT

Purpose: To describe the first reported case of outer retinal damage following the use of Membrane Blue Dual for epiretinal membrane (ERM) surgery.
Observations: A 74-year-old female underwent pars plana vitrectomy and ERM peeling assisted with Membrane Blue Dual for an idiopathic ERM. Postoperatively, the patient reported a decline in visual acuity with a central scotoma. Fundus examination revealed a well-defined retinal whitening in the peeling area which evolved into pigmentary changes as confirmed by fundus autofluorescence. Optical coherence tomography (OCT) showed loss of outer retinal layers and irregular mottling of the retinal pigment epithelium. Fundus and OCT appearance remained unchanged after 4 months and the central scotoma also persisted.
Conclusions and Importance: ERM surgery assisted with Membrane Blue Dual can induce major changes in retinal pigment epithelium and outer retinal layers. This adverse event which probably results from combined light and dye toxicity should be considered by all surgeons even though its occurrence is rare.

1. Introduction

Intraocular vital dyes have become very useful tools to identify ocular tissues during vitreoretinal surgery and thus facilitate complete and less-traumatic removal of epiretinal membrane (ERM) and internal limiting membrane (ILM). While indocyanine green (ICG) has been identified to cause retinal toxicity, Brilliant Blue G (BBG) and Trypan Blue (TB) have become alternatives to ICG because of their affinity for ILM and ERM respectively and their relatively non-toxic and safe profiles.[1,2] However, recent reports have demonstrated RPE and photoreceptors damage following BBG and TB exposure for macular hole surgeries.[3–7] We report the first case of similar outer retinal lesions after epiretinal membrane surgery.

2. Case report

A 74-year-old pseudophakic female presented with a 6-month history of decreased vision and metamorphopsia in the right eye secondary to an idiopathic epiretinal membrane. On examination, her best-corrected visual acuity (BCVA) was 20/40 on the right eye and 20/20 on the left eye, with an axial length of 25 mm on both eyes. Dilated ophthalmoscopic examination demonstrated an ERM resulting in vascular tortuosity in the right eye with unremarkable retinal periphery. Spectral-domain optical coherence tomography (OCT) showed an ERM with loss of foveal pit, inner nuclear layer cysts and an increased central macular thickness (CMT) at 495 μm without anomaly of the retinal pigment epithelium (RPE) (Fig. 1A). Fundus autofluorescence did not reveal any alteration of macular pigment distribution. A 25-gauge transconjunctival pars plana vitrectomy was performed one month later under general anesthesia due to claustrophobia. The Constellation® Vision System (Alcon Laboratories, Fort Worth, Texas, USA) with a Xenon light probe at 40% intensity was used, as well as a panoramic lens and a flat contact lens for respectively wide-field and macular visualization. Following core vitrectomy, as posterior vitreous detachment was already done, ERM was stained using a mix of 0.25 mg/mL brilliant blue G, 1.5 mg/mL trypan blue and 4% polyethyleneglycol (Membrane Blue Dual, DORC Netherlands) in a fluid-filled cavity. The microscope light was turned off during the staining period, then the dye was thoroughly washed off after 1 min. An asymmetrical end-grasping forceps was used to peel off the ERM, but it appeared to be unusually adherent and brittle so that its complete removal was difficult and required two further stainings of 30 seconds each time. The operative

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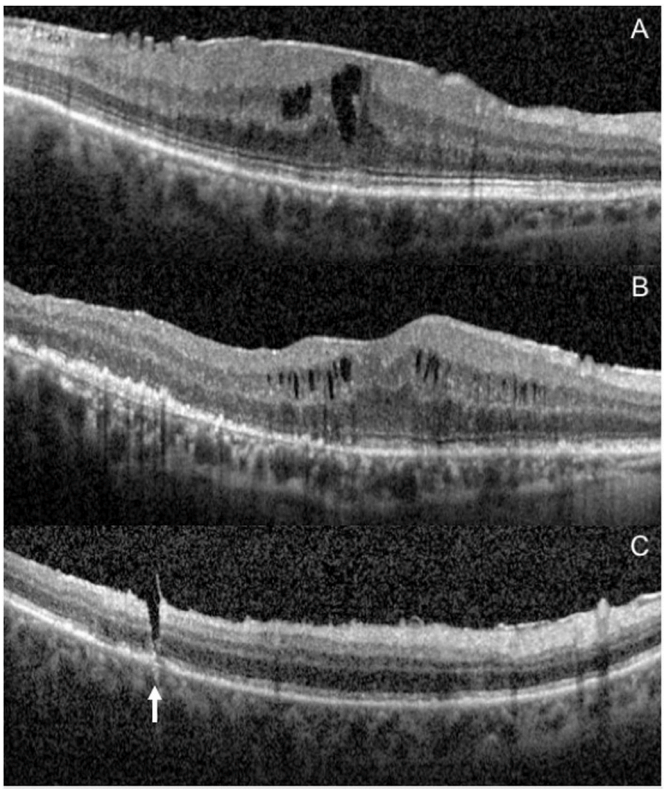

Fig. 1. Optical coherence tomography (OCT) images: (A) Preoperative aspect of the epiretinal membrane (ERM) showing loss of foveal pit, inner nuclear layer cysts and an increased central macular thickness. Note the continuous retinal pigment epithelium (RPE) line and normal outer retinal layers. (B) OCT at 1 month postoperatively shows irregular thickening of the RPE with hyperreflective subretinal deposits and loss of outer retinal layers. (C) An extracentral macular hole is observed where the peeling was started in the upper temporal macula (white arrow).

report mentions a mechanical trauma in the upper temporal macula where the peeling was initiated that led to a localized retinal hemorrhage with retinal whitening. No retinal petechiae were observed elsewhere which would indicate that the ILM beneath the ERM was simultaneously peeled. No subretinal passage of the Membrane Blue Dual (MBD) was observed intra-operatively. Intraocular pressure was maintained at 20 mmHg during the surgery. Sclerotomies were sutured and no tamponade was used. The total surgical time was 111 minutes. One week after surgery, the BCVA had deteriorated to 20/80 with central scotoma. Fundus examination revealed a well-defined retinal whitening in the peeling area (Fig. 2A) corresponding to focal disruptions of the ellipsoid zone on OCT. This area appeared slightly hyperautofluorescent with well-delineated borders on fundus autofluorescence (Fig. 2B). An extracentral macular hole had formed at the location of the retinal trauma (Fig. 1C). At one month, the whitening area had been replaced by a mottled hypopigmented and hyperpigmented appearance involving the macula over about 7-disc diameters (Fig. 2C). Fundus autofluorescence (FAF) showed a well-defined area of hypo- and hyperautofluorescence extending slightly beyond the area of peeled ERM (Fig. 2D). OCT showed loss of outer retinal layers and irregular thickening of the RPE with subretinal deposits (Fig. 1B). The extracentral macular hole had closed spontaneously. Visual acuity improved to 20/40 at 1 month and then to 20/20 at 2 months postoperative. This could be explained by a relative foveolar sparing of the outer retinal lesions. However, the central scotoma persisted as shown in the Humphrey 24-2 and 10-2 visual field automated (Fig. 3A and B). Fundus and OCT appearance remained unchanged 4 months after surgery.

3. Discussion

Chromovitrectomy has become a popular technique in recent years as it facilitates the fine removal of intraocular membranes during vitreoretinal surgery.[8] Several publications have reported damage to the neurosensory retina and retinal pigment epithelial cells, as well as optic nerve atrophy after the use of ICG.[9–14] Therefore, BBG and TB were used as an alternative with a good safety profile demonstrated *in vitro* and *in vivo*.[15–18] Membrane Blue-Dual (MBD) contains a combination of 4% polyethyleneglycol (PEG) to facilitate sedimentation on the retina, 0.025% Brilliant Blue G (0,125 mg) and 0.15% Trypan Blue (0,75 mg) and has a heavier molecular weight than TB or BBG. Although commonly used because of its high level of purity and favorable biocompatibility,[19,20] several cases of decreased BCVA and outer retinal damage following macular hole surgeries using TB, BBG or MBD have been published.[3–7] The described lesions were mottled hypo- and hyperpigmented spots on fundus examination corresponding to areas of hypo- and hyperautofluorescence, thinning of outer retinal layers and RPE, and loss of choriocapillaris on OCT. These areas of retinal damage corresponded to the areas of ILM peeling in all cases. The retinal lesions that we report were noted primarily at the level of RPE cells and photoreceptors, very similar to those described previously. Several well-known risk factors for such toxicity were found in our case. Difficulties of peeling led to a long operating time with repeated staining and total exposure time to MBD was then relatively long as it reached 2 minutes. However, contrary to previous publications and for the first time to our knowledge, toxicity occurred after epiretinal membrane surgery. One of the previously suggested hypotheses was the deleterious effect of ILM peeling, since all reported cases required ILM peeling and the retinal lesions were confined to the peeling area. The authors suggest that the ILM acts as a barrier and the retina bare of ILM could be more susceptible to damage when exposed to repeated staining.[7] Recently, Shen et al. found that both MBD and TB were toxic to human Müller cells with greater toxicity of MBD.[21] Given the ends of Müller cells are integrally associated with ILM, these cells may be vulnerable to damage from dye when in contact with the ILM or the retina bare of ILM. In our case, the surgeon did not mean to peel the ILM and then only peeled one membrane. However, several studies revealed the presence of long segments of ILM on histological specimens of ERM in 70–77% of cases.[22–24] Hence most epiretinal membrane surgeries lead to ILM peeling whether intentional or not, yet there was no report of dye toxicity in these cases. An alternative hypothesis could be an inconspicuous subretinal migration or diffusion of the MBD through the iatrogenic extracentral macular hole.[25] Indeed all previous cases were macular holes and the RPE was then directly exposed to the dye. Exposition of bare RPE could then be the common thread of all reported cases. Retinal phototoxicity from the endoilluminator should also be considered. The peak wavelength of the Xenon light we used is 450 nm (range 420–700 nm)[26] and is known to induce damage to the photoreceptors and mainly to the RPE cells.[27] The increased absorption of the Xenon light by the MBD and changes in the emission spectra of the MBD can produce toxic free radicals and subsequent damage to the RPE cells and photoreceptors. Balaiya et al.[28] demonstrated that BBG at the concentration of 0.25 mg/mL had cytotoxic effects on human RPE cells (ARPE-19) *in vitro*. These effects were directly correlated with exposure time to Xenon endoillumination and inversely correlated with its intensity. Indeed, a significant toxicity was reported after 5 minutes of focal high illumination and after 15 minutes of medium diffuse illumination. Since this phototoxicity is time-related, a long surgical time such as the one we report is probably an important risk factor. Thus, we cannot exclude that a shorter operation time would have prevented this complication. Morphologically, endoilluminator-induced lesions have been described as rounded due to the shaped tip of the light probe and appear superior or inferior to the fovea with relative sparing of the fovea due to concentrated xanthophylls in the fovea.[29] Pattern of toxicity in this case suggests a combination of phototoxicity and dye toxicity.

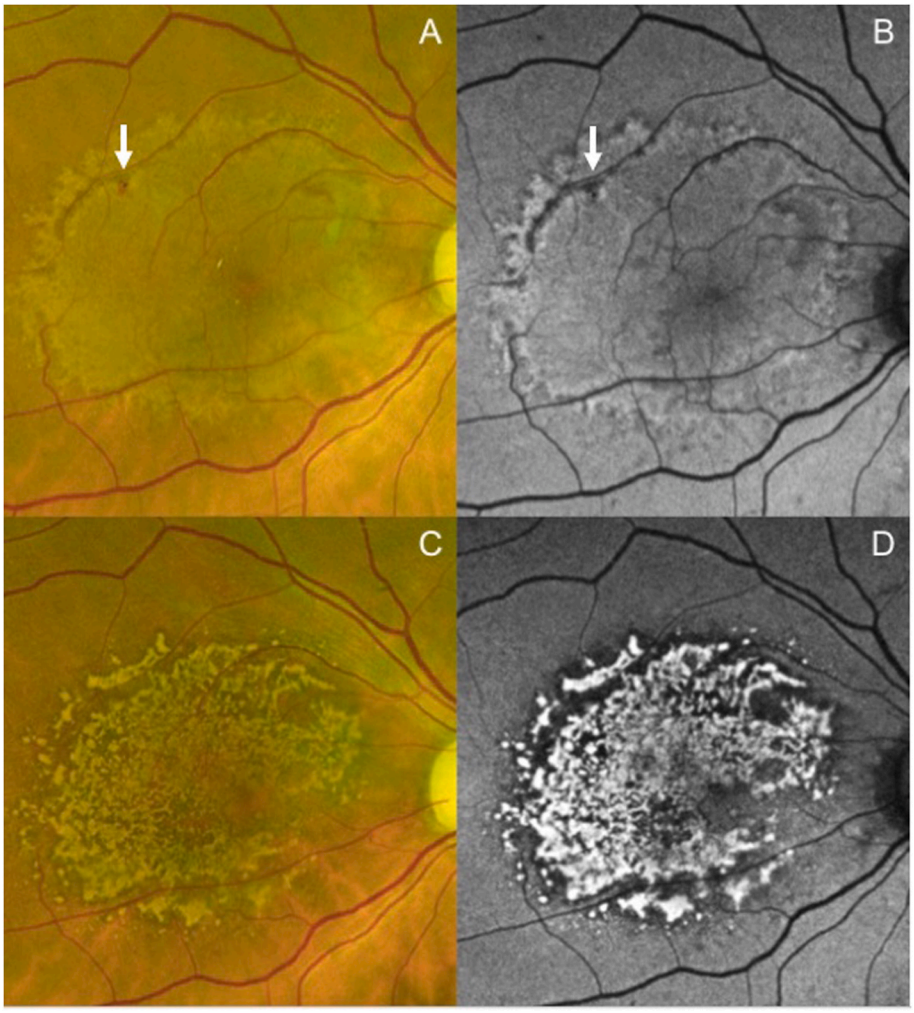

Fig. 2. (A) Fundus photograph at one-week post-op showing a well-delineated area of retinal whitening which corresponds to the peeling area. A punctiform hemorrhage is observed at the location of the peeling initiation (white arrow). (B) Fundus autofluorescence at one week shows an area of well-defined mild hyperfluorescence with few hypofluorescent spots. (C) One month after surgery, fundus photograph shows mottled hypopigmented and hyperpigmented changes extending slightly beyond the peeling area. (D) On fundus autofluorescence at one month, these changes appear as an area of hyper- and hypofluorescence with well-defined borders. Note on both pictures the relative foveal sparing.

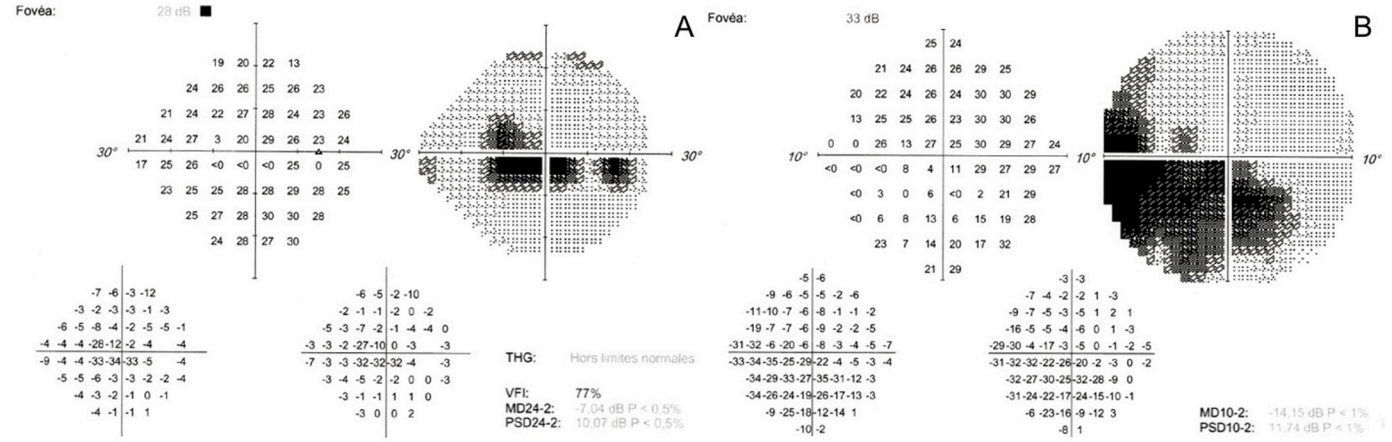

Fig. 3. Two months after surgery, Humphrey 24-2 (A) and 10-2 (B) visual field automated show a central scotoma with relative sparing of the temporal and superior quadrant and a preserved foveal threshold.

4. Conclusion

We here report RPE and photoreceptors damage after the use of MBD following epiretinal membrane surgery. This original case should remind to all surgeons that MBD carries a risk of toxicity even though its occurrence is rare and that repeat staining and high focal endoillumination close to the macula should be avoided. The exposition of bare RPE could be a common thread to all reported cases though the exact mechanism remains to be clarified.

5. Patient consent

Written informed consent was obtained from the patient to publish and report individual patient data.

Authorship

All authors attest that they meet ICMJE criteria for Authorship.

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Declaration of competing interest

The following authors have no financial disclosures: HTV, SLP, AGA, LJ.

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