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CASE REPORT

Retinal toxicity of indocyanine green

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Abstract *Purpose*: To describe a case of scattered toxicity of indocyanine green on the outer retina and retinal pigment epithelium (RPE) after indocyanine green (ICG) assisted membrane peeling for macular pucker. *Methods*: A 61-year-old woman was examined by slit-lamp biomicroscopy, fluorescein angiography (FA), indocyanine green angiography (ICGA) and optical coherence tomography (OCT), 1 month and 1 year after ICG assisted membrane peeling for macular pucker. *Results*: In the absence of significant fundoscopic changes, we have noted on FA and ICGA an occurrence of scattered unusual outer retinal and pigment epithelial changes at the 1- and the 12-month follow-up, probably due to the enhanced phototoxicity associated with the use of ICG at a high concentration (0.5%). *Conclusions*: Retinal toxicity of ICG in macular surgery depends on many factors. In our patient, the retinal changes seem to have been caused by a combination of all the toxic factors. This is the first reported case describing both the angiographic and OCT patterns of diffuse scattered toxicity of ICG on outer retinal layers and pigment epithelium after ICG assisted membrane peeling for macular pucker.

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Introduction

Indocyanine green (ICG) has been recently introduced in macular surgery to facilitate delicate surgical manoeuvres [1, 2], by providing a clear contrast between the internal limiting membrane (ILM) and the retina. The ICG selectively stains the ILM, and peeling of the ILM greatly facilitates peeling the membrane [3], especially when complete removal of epiretinal membranes (ERM) cannot be readily achieved.

Despite the usefulness of this dye, some authors have reported less favourable results in visual acuity, and significant visual field defects, when intraocular ICG was used to assist vitrectomy [1, 4–6]. Therefore, a possible toxic effect of ICG on the different retinal layers has become the subject of several studies.

We report a case of presumed scattered toxicity of ICG on the outer retina and retinal pigment epithelium (RPE) after ICG assisted membrane peeling for macular pucker.

Case report

A 61-year-old woman diagnosed with macular pucker in her left eye was referred to the Department of Ophthalmology of the University of Foggia, for

surgical treatment. She presented with a 6-month history of blurred vision in her left eye. On ocular examination, her best corrected visual acuity (BCVA) was 20/20 in the right eye, and 20/80 in the left eye. Amsler grid was normal in the right eye and revealed marked metamorphopsia in the left eye. Her right eye showed normal appearance on contact lens biomicroscopy, fluorescein angiography (FA) and optical coherence tomography (OCT 3 Stratus; Carl Zeiss Meditec, Dublin, Calif., USA). Contact lens biomicroscopy of the left eye showed a macular pucker with some parafoveal cystic changes (Fig. 1A), and this was confirmed by both FA (Fig. 1B) and OCT.

The patient underwent standard 3 port pars plana near-complete vitrectomy using the Accurus system (Alcon/Grieshaber, Fort Worth, Tex., USA). After this manoeuvre, complete fluid-air exchange was performed, and 0.2 ml ICG at a concentration of 0.5% was injected through a 20-gauge soft-tip silicone cannula into the midvitreous of the air-filled eye. The illumination probe was kept switched on and, 2 min after ICG injection, air–fluid exchange was performed, and residual ICG was removed from the vitreous cavity with suction from the vitreous cutter. Following this, the ERM was incompletely peeled in the macular area using intraocular forceps. Again, complete fluid–air exchange was performed and additional ICG at 0.5% was injected onto the posterior pole to stain the residual ERM and the ILM. As before, we kept the illumination probe switched on and, 2 min after ICG re-injection, air–fluid exchange was performed. The dye in the vitreous cavity was washed out with suction from the vitreous cutter, and then the ILM was removed with ILM forceps.

A week after left eye surgery, BCVA had improved to 20/40, and both fundoscopy (Fig. 1C) and FA (Fig. 1D) revealed that the macular area was free from ERM. A residual piece of stained membrane, temporal to the fovea was detected, but there were no significant RPE changes.

Postoperative examination of the patient's left eye, after 1 month, showed that BCVA was 20/50, and

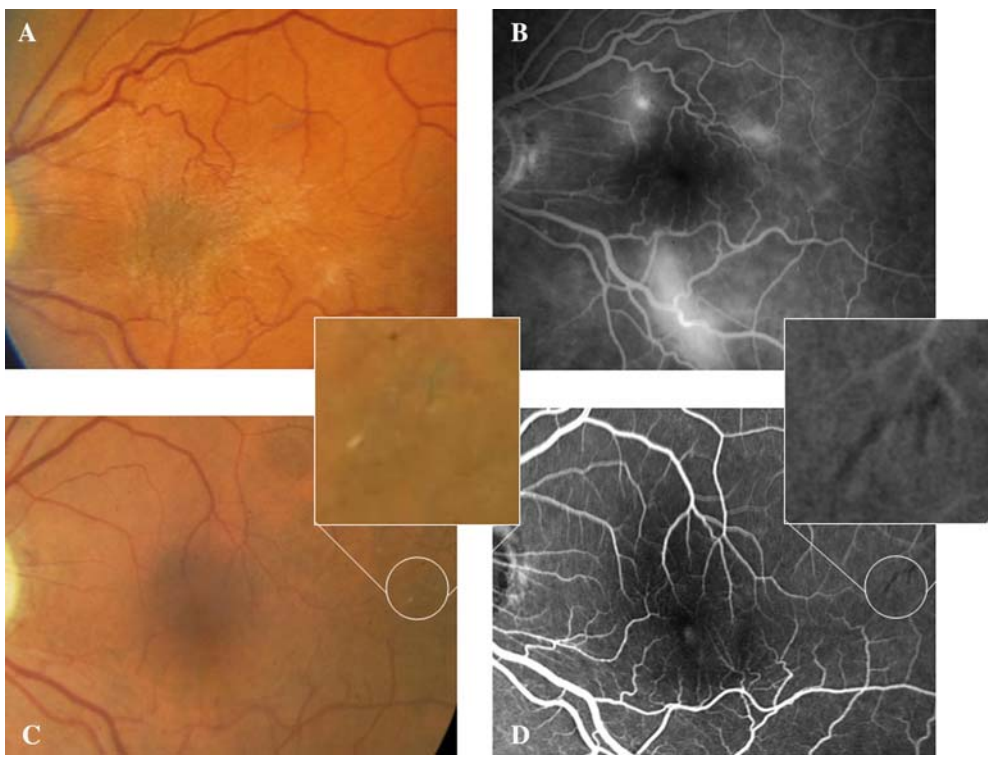

Fig. 1 The fundus colour photograph (**A:** *top left panel*) and the FA (**B**: *top right panel*) of the left eye show the macular pucker before vitrectomy. The fundus colour photograph (**C**: *bottom left panel*) and the FA (**D**: *bottom right panel*) of the left eye show almost normal macular area 1 week after surgery. The smaller *squares* illustrate an enlarged view of a residual piece of stained membrane, temporal to the fovea, both on the fundus colour photograph and the FA

biomicroscopy revealed a normal retina. Surprisingly, the residual piece of stained membrane was still present. FA (Fig. 2, top panel) revealed several hyperfluorescent areas scattered at the posterior pole, mid retinal periphery, and also around the residual stained membrane. No leakage was shown in the hyperfluorescent areas, probably because the lesions were predominantly atrophic. FA of the right eye showed normal appearance (Fig. 2 bottom left panel). ICG angiography (ICGA) was performed, showing late hypofluorescent lesions scattered at the posterior pole and the mid periphery (Fig. 2 bottom middle panel). OCT 3 scans revealed slight atrophic aspects in the outer retina, with no subretinal fluid (SRF) or intraretinal cysts (Fig. 2 bottom right panel, upper and lower).

These fundoscopic, angiographic and OCT findings were still detectable and remained unchanged even at the 12-month follow-up.

Discussion

In the absence of significant fundoscopic changes, we have noted, on FA and ICGA, an occurrence of scattered unusual outer retinal layers (phoreceptors layer) and pigment epithelial changes.

On FA, no leakage was shown in the scattered abnormal hyperfluorescent areas, probably because the lesions were predominantly atrophic. ICGA revealed late hypofluorescent lesions scattered at the posterior pole and the mid periphery, again, probably because the lesions were predominantly atrophic.

These findings are similar to the late atrophic changes of solar retinopathy, in which retinal injury is determined by photochemical mechanisms and, to a lesser degree, by thermal mechanisms. Thus, our findings are subsequent changes that appeared only at the 1-month follow-up and remained unchanged even at the 12-month follow-up.

The cause of the changes observed postoperatively in this case is unknown. Direct toxicity to the RPE, as reported by Engelbrecht et al. [7], should be excluded in this case, because of the absence of direct contact with the ICG solution.

Retinal toxicity of ICG in macular surgery depends on many factors, such as the concentration of the ICG solution, the length of time before removal of ICG from the eye [8], whether ICG is injected into

Fig. 2 The FA of the left eye 1 month after surgery, shows several hyperfluorescent areas, scattered at the posterior pole, mid retinal periphery, and around the residual stained membrane (*top panel*). The *bottom left panel* displays a normal FA appearance of the right eye. ICG angiography (ICGA) of the left eye shows late hypofluorescent lesions scattered at the posterior pole and in mid periphery (*bottom middle panel*); the residual stained membrane is highlighted by a small circle. OCT scans are illustrated by the *arrows* A and B crossing the hyperfluorescet lesion and the residual stained membrane (*top panel*). OCT 3 shows slight atrophic aspects of the outer retina, and no subretinal fluid (SRF) or intraretinal cysts (*bottom right panel, upper and lower*)

an air-filled or a fluid-filled eye, and the energy density of the illumination [9].

In our patient, we could speculate that the retinal changes may have been caused by a combination of all these factors. We injected ICG at a high concentration (0.5%) into the air-filled eye, twice consecutively. Thereafter, the dye was left in the vitreous cavity, for 2 min each time, leaving the illumination probe switched on. The enhanced phototoxicity associated with the use of ICG was the most likely cause of the retinal changes.

As described by Goldstein et al. [10] in albino rabbits, the ICG seems itself to be potentially toxic to all retinal layers. In our case and in such conditions, it appears that ICG toxicity of the retina could even be detected in human eyes using FA, ICGA and OCT.

We no longer routinely use such a high concentration nor a twice consecutive injection leaving the illumination probe switched on.

To the best of our knowledge, this is the first reported case describing both the angiographic and OCT patterns of presumed diffuse scattered toxicity of ICG on outer retinal layers and pigment epithelium after ICG assisted membrane peeling for macular pucker. Similar findings are described in several choroiditis, such as birdshot retino-choroidopathy, multifocal choroiditis and multiple evanescent white dot syndrome. Indeed, in our patient, there were no inflammatory signs whatsoever, thus we excluded such conditions from the list of possible differential diagnoses.

This is a simple report and we believe that our experience needs to be confirmed throughout further studies.

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