CASE REPORT

Postoperative cystoid macular oedema in a patient on fingolimod

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SUMMARY

We describe the first case of fingolimod-associated bilateral cystoid macular oedema (CMO) following uncomplicated cataract surgery. A 57-year-old woman has been on fingolimod for the past 2 years for the treatment of relapsing–remitting multiple sclerosis. She underwent uneventful consecutive cataract surgery 2 weeks apart. Three weeks following the second cataract operation, she reported gradual-onset blurred vision bilaterally. Examination revealed mildly reduced visual acuity and bilateral CMO. Treatment with topical corticosteroids and non-steroidal anti-inflammatory eye drops, as well as cessation of fingolimod in collaboration with the neurologist, resulted in complete resolution of the CMO. Patients on fingolimod are likely to be at increased risk of developing postoperative CMO.

BACKGROUND

Fingolimod (Gilenya, FTY720) is the first oral medication approved by the US Food and Drug Association (FDA) for the treatment of relapsing forms of multiple sclerosis (MS). It is a sphingosine-1-phosphate (S1P) analogue and was approved in 2010. It reduces lymphocyte recirculation from lymphoid tissue-to-blood and peripheral tissues.¹ Its use has been associated with the development of cystoid macular oedema (CMO) not only in patients with MS,^{2,3} but also in patients following renal transplantation.⁴ The authors describe a case of bilateral CMO associated with fingolimod following consecutive cataract surgery.

CASE PRESENTATION

A 57-year-old woman treated for the past 2 years with fingolimod (Gilenya FTY720) 0.5 mg daily for relapsing–remitting MS developed worsening visual acuity due to cataracts. Her ocular history included narrow anterior chamber angles for which she had received prophylactic peripheral iridotomies. She has had no history or evidence of intraocular inflammation. She has been monitored regularly for ocular side effects of fingolimod since commencing this medication and has not had any problems (figures 1A and 2A). Other than MS she did not suffer from any other medical conditions. There is no history of any other systemic medical conditions and she is not on any other regular medications.

She underwent uneventful bilateral consecutive phacoemulsification surgery with intraocular lens implantation 2 weeks apart, starting with the right eye. Day 1 best corrected visual acuity (BCVA) in each eye measured 20/20. Three weeks following left cataract surgery (ie, 5 weeks post-right cataract

surgery), she reported gradual-onset blurred vision in both eyes. Examination revealed BCVA of 20/30 each eye with quiet anterior chambers and normal intraocular pressures. Dilated fundal examination found bilateral CMO.

INVESTIGATIONS

The CMO was clearly demonstrated on optical coherence tomography (OCT; figures 1B and 2B) with central foveal thicknesses measuring 573 and 478 µm, OD and OS, respectively.

TREATMENT

Topical Voltaren eye drops four times per day were added to topical prednisolone acetate four times per day bilaterally. After consultation with the patient's neurologist, fingolimod was ceased.

OUTCOME AND FOLLOW-UP

At a review of her progress 1-week later, the patient reported slight improvement in vision subjectively. Her BCVA at this visit still measured 20/30 in each eye. Macular OCT showed mild reduction in the intraretinal oedema of the right eye (figure 1C), and moderate reduction in the left (figure 2C). Central foveal thicknesses measured 497 and 404 µm, OD and OS, respectively, at this visit. Systemically, the patient did not develop any new neurological symptoms as a result of stopping fingolimod.

Her BCVA 2 weeks later had improved to 20/25 OD and 20/20 OS. Repeat OCT at this visit revealed residual parafoveal oedema in the right eye (figure 1D). However, intraretinal oedema had completely resolved in the left, with only minor hyper-reflectivity seen in the photoreceptor layer (figure 2D). Central foveal thicknesses at this review measured 332 and 316 µm, OD and OS, respectively. The topical medications were reduced to two times per day for 2 weeks and then stopped. One month later, the patient's visual acuity was 20/20 in each eye, unaided. Her macular OCT demonstrated no recurrence of oedema (figures 1E and 2E), with central foveal thicknesses of 297 and 324 µm, OD and OS, respectively. The patient remains off fingolimod and has been started on dimethyl fumarate (Tecfidera).

DISCUSSION

To the best of our knowledge this is the first reported case of postoperative CMO in a patient on fingolimod for the treatment of MS. Postoperative CMO, also known as Irvine-Gass syndrome, is the leading cause of visual loss

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Figure 1 Macular optical coherence tomography (OCT) of the patient's right eye: (A) preoperative scan; (B) 5 weeks post-right cataract surgery, demonstrating cystoid macular oedema (CMO) with a corresponding central foveal thickness of 573 μm ; (C) 6 weeks post-right cataract surgery, demonstrating slightly improved macular oedema, with a corresponding central foveal thickness of 497 μm ; (D) 8 weeks post-right cataract surgery, demonstrating residual parafoveal cysts, with corresponding central foveal thickness of 332 μm ; (E) 12 weeks post-right cataract surgery, demonstrating complete resolution of CMO, with corresponding central foveal thickness of 297 μm .

following uncomplicated cataract surgery.⁵ It typically occurs 4–6 weeks following cataract extraction, and can be detected on fundus fluorescein angiography or macular OCT even in asymptomatic patients.⁶ Resolution can occur spontaneously without additional treatment, but in symptomatic patients, topical corticosteroids and non-steroidal anti-inflammatory eye drops are usually prescribed, with improvement seen over 4–6 weeks. Refractory CMO may require more invasive interventions such as intravitreal administration of corticosteroids or antivascular endothelial growth factor or a formal vitrectomy.

Figure 2 Macular optical coherence tomography (OCT) of the patient's left eye: (A) preoperative scan; (B) 3 weeks post-left cataract surgery, demonstrating cystoid macular oedema (CMO) with a corresponding central foveal thickness of 478 μm ; (C) 4 weeks post-left cataract surgery, demonstrating significantly improved macular oedema, with a corresponding central foveal thickness of 404 μm ; (D) 6 weeks post-left cataract surgery, demonstrating resolved macular oedema with residual subfoveal hyper-reflectivity. The corresponding central foveal thickness was 316 μm ; (E) 10 weeks post-left cataract surgery, demonstrating complete resolution of CMO, with corresponding central foveal thickness of 324 μm .

The use of systemic fingolimod is also associated with CMO. The earliest report of this complication was in a series of patients on fingolimod following renal transplantation.⁷ The incidence has been reported to be dose dependent and ranges between 0.4% and 1% of patients.⁸ Most cases develop within 3–4 months of initiation of therapy and resolve or improve with discontinuation of the drug.^{3 4 8} Fingolimod is a structural analogue of S1P, a lysophospholipid that plays a key role in T-lymphocyte trafficking.¹ Its mechanism of action in the treatment of MS is by binding to the S1P receptor on the T-lymphocyte surface, resulting in receptor internalisation and

degradation, and preventing T-lymphocyte signalling.^{8 9} T-lymphocytes, therefore, remain sequestered in lymph nodes and are unable to participate in the central nervous system autoimmune attack that characterises MS.^{8 9} The S1P receptor also has an alternate function—that of promoting endothelial integrity. It is this function that is believed to be involved in the mechanism of macular oedema.⁸ The S1P acts on the cytoskeleton and intercellular junctions of endothelial cells to enhance barrier function, and degradation of the receptor may lead to increased vascular permeability.⁸

In this patient, the underlying mechanism of CMO is believed to be a combination of fingolimod and cataract surgery, rather than either mechanism alone. The typical onset of CMO associated with fingolimod is at 3 months, whereas this patient has had 2 years of fingolimod therapy without any ocular complications. Similarly, if the CMO was related to cataract surgery alone, then cessation of fingolimod should not see such a rapid resolution of the oedema. We hypothesise that cataract surgery rapidly increased the intraocular levels of proinflammatory mediators (mainly prostaglandins) due to break down of the blood–aqueous barrier,¹⁰ thereby providing the necessary stimulus in

an eye already vulnerable to increased vascular permeability due to the inhibition of S1P by fingolimod, resulting in CMO.

In conclusion, cataract surgery in patients on fingolimod for the treatment of MS could be complicated by increased risk of postoperative CMO. Careful evaluation of the patient's medical history and medications preoperatively could prepare the surgeon for the possibility of this complication and its deviation from typical pseudophakic CMO, thereby preventing a potentially sight-threatening postoperative event. Collaboration with the treating physician in this setting is also critical to the preservation of the patient's systemic well-being.

Contributors The authors declare that each author has contributed significantly to the completion of this case report. JC-CFG was responsible for the interpretation of the investigations, manuscript preparation, literature search and finalisation of the manuscript. MC was responsible for conception of the case report, acquisition of the data, and review and finalisation of the manuscript.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- Fingolimod is a sphingosine-1-phosphate analogue approved for the treatment of relapsing–remitting multiple sclerosis.
- Cystoid macular oedema (CMO) is a potentially sight-threatening condition, and increased incidence of CMO is seen both in patients on treatment with fingolimod, and as a postoperative complication following cataract surgery.
- Treating ophthalmologists and physicians must be wary that patients who are on fingolimod are likely to be at increased risk of developing CMO postcataract surgery, even if they have not suffered from fingolimod-related CMO previously.
- Treatment of CMO in this scenario may require a combination of cessation of fingolimod and topical anti-inflammatory therapy, and collaboration between the treating ophthalmologist and physician is critical.

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