Spectral-domain optical coherence tomography and fluorescein angiography features of cystoid macular edema with serous retinal detachment secondary to intracameral cefuroxime administration

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We present 3 cases of acute-onset cystoid macular edema (CME) with serous retinal detachment (RD) attributable to intracameral injection of a standard dose of cefuroxime at the end of uneventful cataract surgery. Other possible causes of CME, such as diabetic retinopathy, retinal vascular occlusion, uveitis, choroidal neovascularization, vitreomacular traction, and concomitant medications, were excluded. The clinical features seen in the spectral-domain optical coherence tomographic and angiographic patterns of this particular retinal disorder are compared with those reported in the literature. To our knowledge, this is the first reported spectral-domain optical coherence tomographic–documentation of a serous RD that extends beyond the vascular arcades secondary to intracameral cefuroxime administration. The pathogenetic mechanism that leads to this particular retinal abnormality is discussed.

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Cefuroxime is a second-generation cephalosporin active against gram-positive cocci, gram-negative bacilli, anaerobes, and some spirochetes. Because of its wide spectrum of activity, intracameral cefuroxime at a concentration of 1 mg/0.1 mL at the end of cataract surgery was recommended by the European Society of Cataract and Refractive Surgeons. There is some evidence in the literature of ocular toxicity due to overdose of intracameral cefuroxime in complicated and uneventful anterior segment surgery. We describe 3 cases of acute-onset CME associated with extensive serous retinal detachment (RD), presumably attributable to a standard intracameral cefuroxime dose at the end of uneventful cataract surgeries.

CASE REPORTS

Two expert surgeons (F.B., M.S) performed the 3 cataract procedures on 3 different days, in 2 different hospitals, and in 2 different operating rooms. The staff that took part in the surgeries was different for each case.

Surgery was performed using an Infiniti phacoemulsification unit (Alcon Laboratories, Inc.) with a stop-and-chop technique and in-the-bag implantation of a foldable intraocular lens (IOL) (Table 1). At the end of the procedure, 0.1 mL of cefuroxime solution (batch number 1516b) was injected into the anterior chamber. A 50 mg commercial vial of cefuroxime solution for ophthalmic use (Aprokam 50 mg) was used for each patient (Table 1). A trained nurse under the supervision of a second nurse diluted the cefuroxime. The flip-off cap of the vial was removed and the outer part of
the rubber stopper disinfected, and 5 mL of sterile sodium chloride 9 mg/mL (0.9%) solution for injection were aseptically injected into the vial to obtain the proper concentration of 1 mg/0.1 mL. The vial was gently shaken, and then 0.1 mL of the solution was aseptically aspirated with a 1 mL sterile syringe. The surgeon checked the proper amount of drug in the syringe before intraocular administration.

No substances except the infusion fluid (balanced salt solution) and the ophthalmic viscosurgical device (IOL-F) entered the eye during the 3 surgeries. Drug history was negative for concomitant medications with a known retinal toxicity.

Spectral-domain optical coherence tomography (SD-OCT) examination was performed with the Angiovue OCT (RTVue XR Avanti, Optovue, Inc.) or the tomographic-angiographic device (Spectralis HRA + OCT, Heidelberg Engineering GmbH). Fluorescein angiography was performed with the tomographic-angiographic device in patient 1 only. No patient showed relevant signs of anterior chamber and/or vitreous inflammation at the slitlamp examination. Topical betamethasone sodium phosphate 3 mg–naphazoline nitrate 4.5 mg–tetracline hydrochloride 30 mg combination eyedrops and topical diclofenac 1 mg eyedrops were administered 4 times a day for 1 week in all patients.

Case 1

A 56-year-old man had uneventful phacoemulsification surgery with IOL implantation in the left eye at the Department of Ophthalmology, University of Sassari, on December 17, 2015. Eight similar procedures were performed on the same day.

The patient’s systemic and ophthalmic histories were unremarkable. The preoperative corrected visual acuity (CDVA) and refractive error were 20/40 and –3.25 diopters (D), respectively, in the left eye. The anterior segment and fundus were normal in both eyes.

On the first postoperative day, the CDVA in the left eye was 20/250. Fundus examination and SD-OCT showed CME, involving the outer nuclear layer primarily, with a serous RD extending beyond the vascular arcades (Figure 1). Fluorescein angiography showed no retinal, choroidal, or optic nerve head hyperpermeability. After 1 week of treatment, the CDVA improved to 20/20. The SD-OCT scans showed the resolution of the CME and serous RD, with a persistent focal defect of the photoreceptor outer segment.

Table 1. Intraocular lens and cefuroxime batch number used in the 3 patients.

| Case | IOL Name (model number) | IOL Power (D) | Cefuroxime Batch Number |
|------|-------------------------|---------------|------------------------|
| 1    | Acrysof IQ (SN60WF)     | +21.0         | 1516b                  |
| 2    | Acrysof single piece    | +21.0         | 1501b                  |
| 3    | Acrysof single piece    | +10.5         | 1501b                  |

IOL = intraocular lens

A 54-year-old man had uneventful phacoemulsification surgery with IOL implantation in the right eye at the Sardinian Ophthalmic Center, Sassari, on December 21, 2015. Six similar procedures were performed on the same day.

The patient’s systemic history was positive for hepatitis C virus; the ophthalmic history was unremarkable. The CDVA and refractive error were 20/32 and –1.50 D, respectively, in the right eye. The anterior segment and fundus were normal in both eyes.

On the first postoperative day, the CDVA in the right eye was 20/40. Fundus examination and SD-OCT showed CME in the outer nuclear layer, with an extensive shallow serous RD involving the macula and the area around the optic disc (Figure 2). After 1 week of treatment, the CME resolved completely and the CDVA improved to 20/20.

Case 3

An 82-year-old woman had uneventful phacoemulsification surgery in the right eye at the Sardinian Ophthalmic Center, Sassari, on January 7, 2016. Six similar procedures were performed on the same day.

The patient’s systemic history was unremarkable; the ophthalmic history was positive for pathologic myopia. The preoperative CDVA and refractive error were 20/63 and –10.0 D, respectively, in the right eye. The patient’s anterior segment was normal in both eyes. Fundus examination revealed extensive atrophic maculopathy in both eyes.

On the first postoperative day, the CDVA in the right eye was 20/320. Fundus examination and SD-OCT showed CME involving the outer nuclear layer, with an extensive shallow serous RD (Figure 3). After 1 week of treatment, the CME resolved completely and the CDVA improved to 20/25. A subfoveal focal defect of the photoreceptor outer segment was evident.

DISCUSSION

Cefuroxime retinal toxicity is usually associated with a drug overdose or with a complicated cataract surgery when a breakdown of the barrier between anterior and posterior segments has occurred.1,4–7 Some authors have described cases of retinal toxicity presumably attributable to a standard dose of intracameral cefuroxime after uneventful cataract surgery. In those reports, intracameral cefuroxime was diluted from a 750 mg vial, leaving room for a possible dilution error.8,9 In each of our cases, a 50 mg commercially approved vial was used and the dilution was made by a trained nurse and double checked. This makes the chance of a dilution error very unlikely, although not impossible.

The hallmark of cefuroxime retinal toxicity is acute-onset CME with serous RD that appears in the first 24 hours after surgery and significantly decreases the visual function. Optical coherence tomographic findings show that the CME is located in the outer nuclear layer with an intact outer plexiform layer. Some authors define this SD-OCT finding as a schisis rather than...
than a true macular edema. The serous RD appears as a shallow irregular elevation of the photoreceptor layer that involves the entire posterior pole, extending beyond the vascular arcades (Figure 1, B), and appears as a uniform hyporeflective band without debris. Our SD-OCT findings are in line with those reported by Le Du et al., who used SD-OCT and fluorescein angiography and documented 6 cases of early macular edema after phacoemulsification and a suspected overdose of cefuroxime. In previous studies in which fluorescein angiography was performed, the evidence of diffuse leakage in the macular area suggests a blood–retinal barrier breakdown.

In our cases, as in those reported by Faure et al., fluorescein angiography showed no retinal or choroidal hyperpermeability. These findings indicate that structural damage to the neurosensory retina rather than an inflammatory response may have been the cause of the cefuroxime-induced CME. We speculate that a direct toxic effect on the Müller cells

Figure 1. The SD-OCT scans and fluorescein angiography of Case 1 taken at various timepoints. On the left side of each row (A, B, C), infrared images of the posterior pole with green lines show the location of the SD-OCT scans. A: In the middle, the 1-day postoperative SD-OCT shows significant macular edema with associated serous RD. On the right, the early phase of fluorescein angiography. B: In the middle, SD-OCT shows serous RD extending beyond the vascular arcades. On the right, the late phase of fluorescein angiography. C: In the middle, 7-day postoperative SD-OCT shows macular anatomy being restored. On the right, a detail of focal photoreceptor damage.
and the photoreceptor outer segment can explain these tomographic and angiographic patterns. Shahar et al.\textsuperscript{10} showed that at a concentration of 10 mg/0.1 mL, cefuroxime causes retinal damage following administration into rabbit vitreous. Histologic findings show mild to severe structural damage that manifests as loss of photoreceptor outer segments, disorganization of the layered retinal structure, and retinal thinning. The electroretinogram results of animal experiments and human clinical observation show cefuroxime is toxic to the retina and may affect Müller cell function.\textsuperscript{9} It is clear that macular edema induced by cefuroxime represents a specific pathogenic entity, similar to another form of retinal toxicity (niacin maculopathy) rather than to post-surgical CME.\textsuperscript{9} This hypothesis is supported by the lack of perifoveal capillary leakage and petaloid dye accumulation in our patient, suggesting a completely different pathogenetic mechanism.

Another important feature of cefuroxime-induced macular edema, evident in our patients as in similar reports in the literature,\textsuperscript{4,5,8,9} is the complete regression in 1 week. We do not think the dramatic improvement is due to therapy but rather that it occurs spontaneously after the intraocular concentration of the drug has decreased. Cefuroxime levels in the aqueous humor have been shown to decrease 4-fold within 60 minutes of injection.\textsuperscript{11} The reduction in intraocular cefuroxime levels correlates with an anatomic and functional restoration, as reported in animal and humans models.\textsuperscript{11} In 2 of our patients, a photoreceptor outer-segment defect was detected in SD-OCT scans, despite complete resolution of the CME and improvement in visual acuity after 1 week (Figures 1, C, and 3, C). We did not find similar features in the literature, but we think this hallmark can prove that photoreceptors are a possible target for cefuroxime toxicity.

The 3 patients had surgery on different days, in different hospitals, and by 2 different surgeons. Each of them represented 11\% to 17\% of all the phacoemulsification surgeries performed on the same day. We do not know whether “subclinical” SD-OCT alterations were present in other patients who had the same procedure on the same day and in whom visual acuity was not affected because we did not perform SD-OCT in this subset of patients. However, the 3 cases were concentrated in a relatively short period, and

Figure 2. The SD-OCT scans of Case 2 taken at various timepoints. A: Preoperative. B: One day after surgery. C: Seven days after surgery.
we do not have evidence of similar cases occurring in the previous or the following period. For this reason, the 3 cases can be considered a small cluster.

We did not find other factors that might have induced the early postoperative CME in any of our patients. There was no evidence of ocular comorbidities such as diabetic retinopathy, retinal vascular occlusion, uveitis, macular degeneration, or vitreomacular traction. Drug history was negative for concomitant medications with a known retinal toxicity. No substances with a possible toxic effects were used during the cataract surgeries. For these reasons and because the structural features detected in our patients by SD-OCT match those reported by other authors in similar cases, we strongly suspect a direct correlation between the use of intracameral cefuroxime at the end of surgery and the early retinal abnormalities.

In conclusion, retinal toxicity induced by intracameral cefuroxime is more often due to a drug overdose, even though it can also follow a standard dose administration. Despite the severity of the early clinical findings, the resolution of intraretinal and subretinal fluid seems to be complete and usually takes a few days. Some degree of structural outer retinal damage can persist.

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Figure 3. The SD-OCT scans of Case 3 taken at various timepoints. A: Preoperative. B: One day after surgery. C: Seven days after surgery.
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