

Retinal Cases & Brief Reports

Hyper-acute pseudophakic macular edema vanishing within 72 hours: a case series. --Manuscript Draft--

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Abstract:	Purpose : To report three cases of massive pseudophakic macular edema occurring the day after uneventful cataract surgery and resolving in 24-72 hours. Observations : A 68-years woman affected by systemic lupus erythematosus and antiphospholipid syndrome displayed massive macular edema on OCT scan one day after uneventful cataract surgery. Routine postoperative topical eye drops (Chloramphenicol/Betamethasone QID and Bromfenac BID) were continued without additional medications. Three days later OCT showed a completely recovered, normal fovea. Two similar cases were documented. A 73-year-old man and a 53-year-old man underwent cataract surgery and started the mentioned topical postoperative therapy. Severe macular edema was diagnosed the day after surgery and resolved in 24 and 48 hours, respectively. Conclusions : Massive macular edema may occur immediately after uncomplicated cataract and then disappear within 1 to 3 days, without invasive therapies. This is a very significant event that may follow cataract surgery that was previously unreported.
Response to Reviewers:	AUTHOR RESPONSE TO REVIEWERS COMMENTS REVIEWER #1 1. "Previous similar reports have attributed acute, severe CME to intracameral cefuroxime toxicity. Notably, cefuroxime was used in the cases reported herein. Could there have been a compounding error? This might be worth addressing in the discussion. A couple of relevant references are listed below." We thank the reviewer for pointing this out. We modify the discussion as follow: "Acetylcholine (10 mg/ml; Miochol-E, Bausch & Lomb) and cefuroxime (1 mg/0.1 ml;

	Aprokam, Thea Pharma) were separately injected in the anterior chamber at the end of surgery. It has been hypothesized that intraocular cefuroxime might induce postoperative macula edema. Out of 13 patients receiving by mistake cefuroxime at high concentration (9 mg/0.1 ml), 6 patients developed postoperative macular edema.¹¹ Another recent article reported on CME after routine cataract surgery terminated with 3 to 7 mg of cefuroxime.¹² It is possible that cefuroxime toxicity could be the lead factor also in our case series, due to high concentration or excessive susceptibility to the medication. However, the commercial formulation of cefuroxime for intraocular use makes unlikely improper dilution (the powder is content in a 10 ml vial and should be reconstitute simply by addition of 5 ml of saline)." (pages 6-7; lines 129-139) 11. Wong DC, Waxman MD, Herrinton LJ, Shorstein NH. Transient macular edema after intracameral injection of a moderately elevated dose of cefuroxime during phacoemulsification surgery. JAMA Ophthalmol. 2015;133(10):1194-1197. 12. Spackman W, Raman V. Acute exudative serous macular detachment with intraretinal oedema following uncomplicated phacoemulsification cataract surgery. BMJ Case Rep. 2022;15(5):e247772. doi:10.1136/BCR-2021-247772 2. "Would also be good to know if the first patient with lupus had a history of uveitis." We agree with the reviewer since we mistakenly omitted this information. The patient did not experienced any previous inflammatory eye disease so we added the line "with a non-contributory ocular history" (page 4; lines 63-64)
Additional Information:	
Question	Response
Has your manuscript been previously submitted to and/or rejected by another journal?	No
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To the kind attention of
Alexander J. Brucker, MD
Editor-in-Chief
Retinal Cases & Brief Reports

Rome, July 26th, 2022

Dear Dr. Brucker,

We like to thank you and the reviewer for revising our manuscript entitled "Hyper-acute pseudophakic macular edema vanishing within 72 hours: a case series." We carefully considered reviewer's comments and we modified the article according to suggestions raised. Please now accept our point-by-point response and the new version of the paper for evaluation for publication on Retinal Cases & Brief Reports.

AUTHOR RESPONSE TO REVIEWERS COMMENTS

REVIEWER #1

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We really hope to meet the high standards of your Journal and look forward to hearing from you.

Best regards,



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1 **Hyper-acute pseudophakic macular edema vanishing within 72 hours: a case series.**

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3 Antonio Di Zazzo¹, MD, Marco Coassin¹, MD PhD

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7 None of the authors has any financial/conflicting interests to disclose.

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9 Running title: Hyper-acute CME after cataract surgery

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21 **Key words:** Case series; Hyper-acute onset; Pseudophakic cystoid macular edema; Uneventful
22 cataract surgery

23

24 **Summary Statement:** Three cases of massive pseudophakic macular edema, with hyper-acute
25 onset after routine cataract surgery and resolution in 24-72 hours, without invasive therapies.

26

27 **Abstract**

28 *Purpose:* To report three cases of massive pseudophakic macular edema occurring the day after
29 uneventful cataract surgery and resolving in 24-72 hours.

30 *Observations:* A 68-years woman affected by systemic lupus erythematosus and antiphospholipid
31 syndrome displayed massive macular edema on OCT scan one day after uneventful cataract
32 surgery. Routine postoperative topical eye drops (Chloramphenicol/Betamethasone QID and
33 Bromfenac BID) were continued without additional medications. Three days later OCT showed a
34 completely recovered, normal fovea. Two similar cases were documented. A 73-year-old man and a
35 53-year-old man underwent cataract surgery and started the mentioned topical postoperative
36 therapy. Severe macular edema was diagnosed the day after surgery and resolved in 24 and 48
37 hours, respectively.

38 *Conclusions:* Massive macular edema may occur immediately after uncomplicated cataract and then
39 disappear within 1 to 3 days, without invasive therapies. This is a very significant event that may
40 follow cataract surgery that was previously unreported.

41

42

43 **Introduction**

44 Pseudophackic cystoid macular edema (PCME), also known as Irvine-Gass syndrome, is recognized
45 as one of the most common causes of poor visual outcome following cataract surgery.¹ PCME is
46 defined as a retinal thickening of the macula due to the alteration of the normal blood-retinal barrier,
47 with perifoveal retinal capillaries leakage and storage of fluid primarily in the outer plexiform layer
48 (OPL).² Nowadays, optical coherence tomography (OCT) is considered the most sensitive method to
49 detect and monitor CME, playing a key role in its diagnosis and follow up.³ Clinically significant
50 PCME imparting patient's vision is found in 1-2% of patients with its peak 6 weeks following
51 surgery.⁴ Resolution of the macular edema occurs within 3-4 months.⁵ Steroidal and non-steroidal
52 antiinflammatory drugs (NSAIDs) have been proposed for the prevention or the treatment of PCME.⁶
53 Several factors and mechanisms may be involved in the pathogenesis of PCME, including the release
54 of mediators of inflammation after cataract surgery, such as prostaglandins, arachidonic acid,
55 cytokines and vascular endothelial growth factor (VEGF) with the disrupt of the blood-retinal barrier
56 (BRB), leading to increased vascular permeability resulting in macular edema.⁷⁻⁹
57 We herein report three cases of severe PCME occurring one day after uneventful cataract surgery; all
58 patients where routinely under treatment with topical antibiotic, steroidal and NSAIDs eye drops;
59 PCME resolved within 72 hours without additional treatment in all three cases.
60

61 **Case 1**

62 A 63-year-old woman underwent cataract surgery in the right eye. Past medical history was
63 remarkable for systemic lupus erythematosus (LES) and antiphospholipid syndrome (APS) with a
64 non-contributory ocular history. Preoperatively, best corrected visual acuity (BCVA) was 20/80
65 Snellen and no other conditions were present in the right eye. The uneventful surgery consisted in
66 routine phacoemulsification throughout a 2.4 mm clear-corneal incision and implantation of a single-
67 piece acrylic intraocular lens (IOL). The patient was discharged from the outpatient clinic and started
68 on topical therapy the same afternoon after cataract surgery (Chloramphenicol/Betamethasone QID
69 and Bromfenac BID, eye drops).

70 The day after surgery, the patient returned to the clinic complaining of marked decrease in visual
71 acuity in the operated eye. The BCVA in right eye was reduced to 20/400 Snellen. Slit lamp
72 examination showed mild corneal edema and IOL correctly positioned in the capsular bag. The IOP
73 was within normal limits and indirect ophthalmoscopy was unremarkable. OCT scan showed severe
74 pseudophakic macular edema (Fig. 1a). Patient was instructed to continue
75 Chloramphenicol/Betamethasone QID and Bromfenac BID eye drops. Next day patient experienced
76 subjective improvement of visual acuity. Two days after diagnosis of PCME, vision improved to
77 20/25 Snellen and a new OCT scan demonstrated a complete resolution of the macular edema (Fig.
78 1b). At last follow up visit 3 week later, visual acuity was 20/20 Snellen and OCT confirmed the
79 permanent resolution of PCME in the right eye.

80 This case was not isolated. Within two years, a similar pattern was observed in two other patients in
81 our Institution.

82

83 **Case 2**

84 A 73-year-old male patient underwent cataract surgery in the left eye. Past medical history was
85 unremarkable except for a benign prostate adenomyoma. Preoperatively BCVA of the right eye was
86 20/63 Snellen and there was no sign of ocular inflammation at slit lamp examination. Fundus

87 examination showed no retinal diseases. The patient underwent regular cataract surgery. After 24
88 hours, patient complained of significant visual impairment in the operated eye. BCVA decreased to
89 20/125 Snellen. Anterior segment examination was normal with the IOL correctly positioned within
90 the capsular bag. The OCT scan showed severe PCME with subretinal and intraretinal fluid (Fig. 1c).
91 Routine postoperative topical eye drops (Chloramphenicol/Betamethasone QID and Bromfenac BID)
92 were continued. The following day, BCVA improved to 20/25 Snellen and OCT macular scan showed
93 a total disappearance of macular edema (Fig. 1d).

94

95 **Case 3**

96 The last case was reported in a 53-year-old healthy man was that scheduled for cataract surgery in
97 the right eye on March 2021. Preoperative BCVA was 20/50 Snellen and IOP was within normal
98 limits. Routine cataract surgery was carried out without complications. The patient was discharged
99 with the usual postoperative eye drops (Chloramphenicol/Betamethasone QID and Bromfenac BID).
100 After 24 hours, patient returned to our centre complaining of blurred vision in the right eye. BCVA
101 was 20/200 Snellen. Slit lamp examination showed clear central cornea and IOL was well positioned
102 in the capsular bag. OCT scan of the right retina demonstrated moderate macular edema (Fig. 1e).
103 After 2 days, patient reported subjective improvement of visual acuity. BCVA improved to 20/25
104 Snellen and OCT scan displayed a complete resolution of the intraretinal and subretinal fluid (Fig.
105 1f).

106

107

108 Discussion

109 The underlying causes of the formation of CME after cataract surgery are not fully understood.
110 Various hypotheses have been proposed. Mechanical trauma from the surgery may promote the
111 expression of cyclooxygenase, which triggers the synthesis of prostaglandins and other inflammatory
112 mediators.¹⁰ These factors impair the blood–retinal barrier postoperatively, leading to increased
113 permeability of perifoveal capillaries and fluid accumulation in the perifoveal retina.^{7–9}

114 Although the precise mechanisms characterizing the passage of fluid from the bloodstream to the
115 OPL are not known, it is believed that the time required for this mechanism to occur is in the order
116 of weeks and months.^{4,5} In our series, the presence of PCME was documented by OCT the day after
117 cataract surgery and macular edema disappeared within 72 hours in all three cases.

118 We are not able to explain the cause of the sudden genesis and resolution of PCMEs in our patients.
119 In the case of the 63-year-old woman, LES and APS might have had a role in promoting macular
120 edema formation. The defective circulatory homeostasis could have played a role in the early
121 breakdown of the blood-retinal barrier. However, the two other patients presented an unremarkable
122 medical history. In particular, none of them was affected by diabetes.

123 Posterior hyaloid was completely detached from the retina only in the first case, but it was not in the
124 other two eyes, as shown in Figure 1. All three patients presented moderate cataracts with 2+ nuclear
125 sclerosis and no other ocular comorbidities. Intraocular inflammation and anterior chamber flare/cells
126 were not remarkably increased the day after surgery in the three eyes.

127 In all three cases, phacoemulsification was performed throughout a 2.4 mm clear corneal incision
128 (Constellation Vision System, Alcon) without complications, and a one-piece acrylic IOL was placed
129 inside the capsular bag (AcrySof SA60AT, Alcon). Acetylcholine (10 mg/ml; Miochol-E, Bausch &
130 Lomb) and cefuroxime (1 mg/0.1 ml; Aprokam, Thea Pharma) were separately injected in the anterior
131 chamber at the end of surgery.

132 It has been hypothesized that intraocular cefuroxime might induce postoperative macula edema. Out
133 of 13 patients receiving by mistake cefuroxime at high concentration (9 mg/0.1 ml), 6 patients

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137 to the medication. However, the commercial formulation of cefuroxime for intraocular use makes
138 unlikely improper dilution (the powder is content in a 10 ml vial and should be reconstitute simply
139 by addition of 5 ml of saline).

140 Preoperative topical therapy is not routinely prescribed in our hospital nor it was in these patients.
141 Postoperative eye drops (Chloramphenicol/Betamethasone QID and Bromfenac BID) were ordinarily
142 started by all three patients in the afternoon immediately following cataract surgery and drops were
143 continued after the discovery of macular edema. Eye drops seem not to have played a role in
144 preventing the PCME - and therefore in treating it, especially because of the short course of treatment.
145 We can only speculate how a severe form of pseudophakic macular edema may occur hyper-acutely
146 after uncomplicated cataract surgery and then vanish within 1 to 3 days without need of invasive
147 therapies. We believe this is a very significant event that may follow cataract surgery, that was
148 previously unreported and that may be severely underestimated.

149

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186 **Figure Legend**

187 **Figure 1. Three cases of severe PCME occurring one day after uneventful cataract surgery**
188 **and completely resolving within 72 hours.** OCT scan of a 68-years woman, one day after routine
189 cataract surgery showing massive PCME (a), and 72 hours later showing a completely recovered,
190 normal fovea (b). OCT scan of a 73-year-old male patient, one day after uneventful cataract surgery
191 showing subretinal and intraretinal fluid (c), and 24 hours later demonstrating a total disappearance
192 of macular edema (d). OCT scan of the right retina of a 53-year-old man one day after routine
193 cataract surgery demonstrating macular edema (e) and 48 hours later displaying a complete
194 resolution of the PCME (f).

