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Macular Edema After Rhegmatogenous Retinal Detachment Repair: Risk Factors, OCT Analysis, and Treatment Responses.

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Abstract

Purpose: To investigate risk factors, imaging characteristics, and treatment responses of cystoid macular edema (CME) after rhegmatogenous retinal detachment (RRD) repair.

Methods: Consecutive, retrospective case-control series of patients who underwent pars plana vitrectomy (PPV) and/or scleral buckling (SB) for RRD, with at least six months of follow-up. Clinical and surgical parameters of patients with and without CME (nCME), based on spectral-domain optical coherence tomography (OCT), were compared.

Results: Of 99 eyes enrolled, 25 had CME while 74 had nCME. Patients with CME underwent greater numbers of surgeries ($P < 0.0001$). After adjusting for number of surgeries, macula-off RRD ($P = 0.06$), proliferative vitreoretinopathy (PVR) ($P = 0.09$), surgical approach (PPV and/or SB, $P = 0.21$), and tamponade type ($P = 0.10$) were not statistically significant, although they all achieved significance on univariate analysis ($P = 0.001$ or less). Intraoperative retinectomy ($P = 0.009$) and postoperative pseudophakia or aphakia ($P = 0.008$) were more frequent in the CME group, even after adjustment. Characteristics of cCME on OCT included diffuse distribution, confluent cysts, and absence of subretinal fluid or intraretinal hyperreflective foci. Macular thickness improved significantly with intravitreal triamcinolone ($P = 0.016$), but not with anti-vascular endothelial growth factor agents ($P = 0.828$) or dexamethasone implant ($P = 0.125$).

44 After adjusting for number of surgeries and macular detachment, final visual

45 acuities remained significantly lower in the CME vs nCME group ($P = 0.012$).

46 **Conclusion:** Risk factors of CME include complex retinal detachment repairs

47 requiring multiple surgeries, and pseudophakic or aphakic lens status..

48 Although this cCME was associated with poor therapeutic response,

49 corticosteroids were the most effective studied treatments.

50

51 **Keywords:** intravitreal injection; macular edema; retinal detachment;

52 spectral-domain optical coherence tomography; vitrectomy; corticosteroids

53

BACKGROUND

Cystoid macular edema (CME) is a common retinal condition characterized by macular thickening with intra-retinal fluid accumulation, often accompanied by decreased visual acuity (VA) [1]. It may develop as a complication of a wide spectrum of retinal diseases including diabetic retinopathy (DR), uveitis, exudative age-related macular degeneration (AMD), retinal vein occlusion (RVO), and genetic syndromes such as retinitis pigmentosa (RP) [2].

Although the pathophysiology of CME is multifactorial, breakdown of the inner blood retinal barrier is a common endpoint in most cases [1]. Current theories suggest subclinical inflammation as responsible for post-rhegmatogenous retinal detachment (RRD) CME [3]. While progressive leakage may be outlined with fluorescein angiography (FA) as the *gold-standard* for CME diagnosis, optical coherence tomography (OCT) is currently the most common imaging modality in the diagnosis and characterization of CME, as it is non-invasive and provides high resolution cross-sectional imaging of retinal anatomy [4], allowing easier and more frequent follow-up,

Rhegmatogenous retinal detachment is characterized by progressive accumulation of subretinal fluid due to retinal breaks. Although surgical repairs, including scleral buckle (SB) and pars plana vitrectomy (PPV), are effective surgical treatments, some cases with successful reattachment may have poor visual outcomes related to postoperative CME development [5, 6],

77 which may persist for years in a minority of patients [7]. Retrospective and

78 observational studies using FA and OCT have shown rates of post-vitrectomy

79 CME varying from 5.5% after PPV for symptomatic floaters to 40% after

80 complicated detachment repairs [6, 8, 9]. Treatments for CME primarily

81 target inflammatory and pro-angiogenic mediators, but standard therapies

82 such as anti-vascular endothelial growth factor (anti-VEGF) therapies may be

83 ineffective for post-RRD CME [9, 10].

84   There is little data on post-RRD CME risk factors, rates, and anatomical

85 characteristics [3, 5, 11]. Therefore, this observational study was designed to

86 compare a consecutive case series of eyes with *versus* without post-RRD

87 CME, with the aim to determine its risk factors and describe its clinical

88 characteristics and therapeutic outcomes.

89 **METHODS**

90   This was a retrospective, observational study approved by the medical

91 center's institutional review board, University of California Los Angeles Office

92 of Human Research Protection (IRB#16-000574). This study adhered to the

93 tenets of the Declaration of Helsinki and the rules of the Health Insurance

94 Portability and Accountability Act of 1996.

95   Electronic health records (EHR) from a large academic referral center

96 (Stein Eye Institute at UCLA) were reviewed. Current Procedural Terminology

97 (CPT) coding records of surgical procedures from January 2015 to December

98 2017 were queried.

99

100 **Population**

101   All candidates underwent SB, PPV, or combined procedures for RRD,

102 performed by two experienced vitreoretinal surgeons (JPH and SDS), with at

103 least six months of follow up after surgery. Records were evaluated through

104 July 2018.

105   Exclusion criteria were severe ocular trauma, uveitis, DR,

106 endophthalmitis, RVO, myopic retinoschisis, or advanced dry or wet AMD.

107

108 **Spectral Domain-OCT Analysis**

109   All patients diagnosed with CME were examined with eye-tracked OCT.

110 All OCTs were acquired with the Spectralis® (Heidelberg Engineering GmbH,

111 Heidelberg, Germany) and RS-3000 (Nidek® Inc, San Jose, CA) devices. All

112 CME was analyzed with Spectralis® OCTs consisting of 19 horizontal B-scans

113 and manually adjusted for foveal centration. All OCT scans were carefully

114 reviewed independently by two graders (CP, JPH) on the Heidelberg Eye

115 Explorer software (Version 1.10.0.0).

116 A diagnosis of CME was noted if intraretinal hyporeflective spaces were

117 noted in the inner nuclear layer (INL) and/or outer plexiform layer (OPL).

118 Retinal thickness measurements were not used for CME diagnosis, as eyes

119 had varying levels of atrophy.

120 Eyes were classified as having postoperative transient CME (tCME),

121 chronic CME (cCME), or no CME (nCME). Both tCME and cCME were included

122 as all CME (aCME) for statistical analysis. Postoperative tCME was defined as

123 CME seen on OCT within six months of the final RRD, lasting less than six

124 months, and resolving using topical treatment. Postoperative cCME was

125 defined as CME seen on two OCTs at least six months apart, based on

126 previous reports.[12]

127 Recorded characteristics of cCME on OCTs included presence of

128 subretinal fluid, layers of CME involvement, presence of intraretinal

129 hyperreflective foci, and integrity of outer retinal layers. Efficacy of anti-

130 VEGF, triamcinolone acetonide (TA), or dexamethasone implant (Ozurdex®,

131 Allergan Inc, Irvine, California) (DEX) injections were assessed after 4-6

132 weeks, if OCT was available. To determine treatment effect, pre- and post-

133 injection OCTs were analyzed for central subfield thicknesses (CST) and inner

134 macular volumes, comprised of the central five areas of the standard early

135 treatment for diabetic retinopathy study (ETDRS) subfields.[13]

136

137 **Clinical Charts Analysis**

138   Preoperative RRD parameters, intraoperative and post-operative data

139 were collected. Glaucoma was counted if the patient carried this diagnose

140 from a glaucoma specialist. Visual acuity was measured on a Snellen chart

141 and converted to logarithm of the minimum angle of resolution (LogMAR)

142 values for statistical analysis. Count fingers and hand motions vision were

143 recorded as 1.98 and 2.28 LogMAR, respectively, based on previous studies

144 using the Freiburg Visual Acuity Test.[14] Type of cCME treatment and

145 number of intravitreal injections were included.

146 **Statistical Analysis**

147   Qualitative values were listed as ratios and percentages while

148 quantitative values were presented as mean ± standard deviation (SD).

149 Qualitative variables were compared using the Fisher exact test. To compare

150 continuous data between two groups, a Mann-Whitney U test was used. The

151 Wilcoxon signed rank test was used to analyze changes in CST and inner

152 retinal volume. The Kruskal-Wallis test was used to compare pre-injection

153 OCT parameters between groups. The Shapiro-Wilk test assessed the

154 normality of variable distribution. Covariate adjusted differences between

155 CME groups were assessed using regression modeling (i.e. logistic, linear,

156 and multinomial) using the number of surgeries as the covariate. Final visual

157 acuity (logMAR) was log transformed in multivariable analyses and used the

158 additional covariate of macula on/off. All statistics were performed in Stata

159 SE 15.1 (StataCorp LP, College Station, TX). A *P* value of less than 0.05 was

160 considered statistically significant. Denominators of ratios were less than the

161 total number of eyes in the category if eyes could not be included in

162 analyses due to missing or incomplete records.

163   **RESULTS**

164 **Population**

165   A flowchart of population selection is shown in Figure 1. A total of 508

166 surgical records were retrieved using CPT codes from January 2015 to

167 December 2017. Of these, 133 eyes undergoing RRD repair met inclusion

168 and exclusion criteria. Of these, 34 had less than six months of follow-up.

169 The remaining 99 eyes of 97 patients were included for analysis. Of these, 20

170 patients (20%) had cCME, 5 (5%) had tCME, and 74 (75%) had nCME. Our

171 primary analyses examine tCME and cCME as a single group, all CME (aCME),

172 in comparison to nCME due to the small sample size for tCME. Descriptive

173 statistics for all three groups can be found in the supplementary Table S1.

174

175 **CME Risk Factors**

176   Demographic and surgical data are summarized by CME group in Table

177 1. There was no difference in age at last surgery between patients in the

178 aCME group (64.1 ± 11.6 years) *versus* patients in the nCME group (56.7 ±

179 18.0 years, $P = 0.092$). There was no significant difference in gender ($P = $

180 0.093), glaucoma status ($P = 0.258$), or length of follow-up ($P = 0.869$).

181 Among those with glaucoma, there was no difference in the rates of topical

182 prostaglandin analogs, other topical medications, or glaucoma surgery

183 between groups ($P = 0.992$)

184   Eyes in the aCME group underwent a significantly greater number of
185   retinal surgeries (3.5 $\pm$1.8) compared with eyes in the nCME group (1.4 $\pm$
186   1.9) *(P < 0.001)*. Due to the high collinearity between CME status and
187   number of surgeries, multivariate analysis using this as a covariate was
188   performed. Final lens status differed significantly between groups after
189   adjustment *(P* = 0.008), with only one eye in the aCME group remaining
190   phakic. A higher rate of aCME eyes had a macula-off retinal detachment
191   (20/24, 83%), compared with nCME eyes (31/70, 44%, *P* = 0.001).
192   Proliferative vitreoretinopathy (PVR) stage C was more frequent in the aCME
193   group (15/24, 63%) *versus* the nCME group (5/74, 7%), *P* < 0.0001. However,
194   both macula-off status *(P* = 0.06) and presence of PVR C *(P* = 0.09) lost
195   statistical significance after adjustment for the total number of surgeries
196   performed. Surgical approaches were statistically different between the
197   aCME and nCME groups: primary SB in 1/25 (4%) aCME eyes vs 25/74 (34%)
198   nCME eyes, PPV in 7/25 (28%) aCME eyes vs 28/74 (38%) nCME eyes, and
199   combined SB+PPV in 17/25 (68%) aCME eyes vs 21/74 (28%) nCME eyes (*P*
200   < 0.0001). However, these differences in the surgical approach were not
201   reliably different after adjustment for the number of surgeries. Rates of
202   retinectomy were higher in the aCME group than the nCME group after
203   adjustment (9/25, 36% vs 4/74, 5%, *P* = 0.009). Rates of cryotherapy were
204   higher in the nCME group (30/74, 41%) than aCME group (4/24, 17%), even
205   after adjustment *(P* = 0.036). Unadjusted differences in tamponade agent
206   between groups were statistically significant (P < 0.0001). Notably, 16 out of

207   25 (64%) aCME eyes received silicone oil (SO) at least once, while only 4 out

208   of 74 (5%) of nCME eyes did. However, tamponade differences were no long

209   significant after covariate adjustment. There was no difference in the use of

210   perfluorocarbon liquid (PFCL) (P = 0.728).

211   At last examination, VA was significantly lower in aCME group (0.85 ±

212   0.80 LogMAR) than in nCME group (0.20 ± 0.30 LogMAR), P < 0.0001. When

213   adjusting for the number of surgeries and macular detachment, the marginal

214   estimates for between group differences in LogMAR were attenuated (aCME

215   = 0.55 vs nCME = 0.26), though still statistically significant (P = 0.012).

216   Two patients had non-simultaneous RRDs in each eye. One patient was

217   23 years of age at the time of both surgeries and underwent SB with

218   cryotherapy in each eye for inferior chronic RRD, without CME development.

219   The other patient was 83 at the time of final surgery in both eyes, had initial

220   surgeries performed elsewhere, had multiple PPVs in both eyes, and received

221   SO in both eyes, and this patient developed cCME in both eye.

222   **OCT Characteristics of cCME**

223   Eyes in the cCME group (n = 20) shared particular qualities on OCT

224   (Figure 2). All eyes had diffuse CME involving the four macular quadrants.

225   The CME always involved the fovea but had variable extent into peripheral

226   macula and was often asymmetric. Cysts were uniformly present in the INL

227   and OPL, with occasional ganglion cell layer involvement. Florid CME often

228   assumed a retinoschitic appearance. With time, cysts coalesced into larger

229   confluent cavities with irregular, polygonal shapes. These cysts often

230   spanned within the same retinal layer and across adjacent layers. Temporary

231   resolution of these cysts after treatment disclosed disorganization and

232   variable atrophy of the retinal layers in areas of cyst confluency. If CME

233   recurred after treatment, it typically recurred in the same distribution of the

234   macula.

235   Outer retinal layer integrity was heterogeneous. On the first OCT with

236   CME after the final RRD repair, ellipsoid zone (EZ) disruption was seen in 18

237   eyes (90%), external limiting membrane (ELM) disruption in 14 eyes (80%),

238   and retinal pigment epithelial (RPE) disruption in 11 eyes (55%). Remarkably,

239   there was no case with subretinal fluid (SRF), and no case of intraretinal

240   hyperreflective foci or hemorrhage.

241   An epiretinal membrane (ERM) was detectable on OCT during the post-

242   operative follow-up period in 17/20 (85%) cCME eyes, 2/5 (40%) tCME eyes,

243   and 28/74 (38%) of nCME eyes (P = 0.005). Evidence of traction on OCT,

244   such as inner retinal wrinkling or ectopic inner foveal layers, was appreciable

245   in only 4 of the 17 cCME eyes with ERM. However, the severity of CME was

246   out of proportion to the ERM changes in all but one of these four eyes.

247

248   **CME Treatments**

13

249   All patients with tCME (n = 5) and cCME (n = 20) received topical

250   medications. Intravitreal injections and surgical interventions were

251   administered according to physician discretion. All patients received

252   corticosteroid drops, non-steroidal anti-inflammatory agent (NSAID) drop, or

253   a combination of both for at least two months after the diagnosis of CME. If

254   the CME failed to respond, patients thereafter received intravitreal injections

255   of anti-VEGF (bevacizumab, ranibizumab, aflibercept), or steroids

256   (triamcinolone acetate (TA), and/or dexamethasone intravitreal implant

257   (DEX)).

258   The five patients (25%) with tCME had permanent resolution of CME

259   with drops. Table 2 summarizes intravitreal treatments and anatomical

260   responses of cCME. Five patients received at least one bevacizumab

261   (Avastin®, Genentech Inc., San Francisco, CA, USA) injection, and one of

262   these patients also received aflibercept (Eylea®, Regeneron Inc., Tarrytown,

263   NY, USA) injections. In cCME eyes, there was a significant CST (P = 0.016,

264   Wilcoxon signed rank test) and volume (P = 0.016) decrease after TA. (P =

265   0.125) (Figure 3). There was no difference in pre-injection CST or volume

266   between groups (P = 0.397, P = 0.457). There was no significant change in

267   CST or volume with anti-VEGF treatment (P = 0.915, P = 0.828) or DEX (P =

268   0.434, P = 0.125). No patient developed elevated intraocular pressure (IOP)

269   after intravitreal injection requiring treatment. One patient developed sterile

270   endophthalmitis after her seventh TA injection that spontaneously resolved

271 without sequelae. A PPV for an ERM was performed in 9/16 cCME eyes with

272 OCT evidence of ERM, with full resolution of the CME in only one eye.

273

274 Table 2: Treatments for chronic cystoid macular edema (cCME) and

275 anatomical responses on spectral-domain optical coherence tomography.

Type of Treatment	Anti-VEGF	TA	DEX	
Number of Eyes	5	7	4	
Number of Injections (Median; [Range])	2.5, 1-14	2.0, 1-10	2.5, 1-7	
CST pre-injection (μm)	401 ± 84.9	481 ± 104	397 ± 57.0	$P = 0.397$
CST post-injection (μm)	393 ± 106	402 ± 102	355 ± 80.4	
Percent CST change (μm)	-1.44 ± 17.1, $P = 0.915$	-15.6 ± 16.6, $P = 0.016$	-11.0 ± 10.7, $P = 0.434$	
Inner macular volume pre-injection (mm³)	2.81 ± 0.43	3.18 ± 0.56	3.12 ± 0.80	$P = 0.457$
Inner macular volume post-injection (mm³)	2.74 ± 0.53	2.72 ± 0.53	2.66 ± 0.486	
Percent (%) inner macular volume change (mm³)	-2.49 ± 12.35, $P = 0.828$	-13.9 ± 10.8, $P = 0.016$	-10.7 ± 25.7, $P = 0.125$	

276

277 Values are listed as averages with standard deviations. VEGF = vascular

278 endothelial growth factor. TA = triamcinolone acetate. DEX =

279 dexamethasone implant. CST = central subfield thickness.

280

281

282 **DISCUSSION**

283   Chronic CME after retinal detachment repair remains a challenging

284 complication. In this paper, the risk factors for post-RRD CME, its OCT

285 characteristics, and treatments outcomes are described.

286   Chronic post-RRD CME is thought to be pathophysiologically distinct

287 from other etiologies of CME [3]. Among CME etiologies such as uveitis, RVO,

288 and DME, many of the cytokines and damaged tissue responses are shared

289 [1, 2, 15]. Certain CME etiologies, however, may have unique

290 pathophysiologic mechanisms despite phenotypic similarities [16]. Entities

291 with a significant pro-angiogenic component, such as exudative AMD, may

292 respond to anti-VEGF agents, while those with a broad inflammatory

293 component, such as uveitic CME or Irvine-Gass syndrome, may respond

294 better to anti-inflammatory drugs [12].

295   While some studies found no risk factor differences for CME rates [5,

296 17], some series have, on univariate analyses, reported increased rates in

297 pseudophakic [18] and aphakic eyes [6], older patients, more extensive RRD,

298 and a history of a detached macula. In the present study, lens status was

299 significantly different between groups, with increased pseudophakia and

300 aphakia in aCME eyes. Unicameral communication in vitrectomized eyes

301 modifies circulation of inflammatory cytokines, as animal studies have noted

302 changes in oxygen and antioxidant gradients [19]. Higher rates of
303 pseudophakia/aphakia in the aCME group may be related either to the actual
304 lens surgery or to the complexity of the vitreo-retinal surgeries requiring lens
305 extraction. As a substantial proportion of eyes with complicated RRD will be
306 made pseudophakic or aphakic, anticipating CME in complex cases can have
307 prognostic implications.

308   Eyes with CME had a greater number of surgeries, higher rates of PVR
309 grade C and retinectomy, and higher rates of SO use. Many studies have
310 shown increased inflammation and CME with more complicated ocular
311 surgeries and inflammatory risk factors [3, 11, 20]. Re-detachments are
312 frequently associated with PVR formation and warrant additional surgeries,
313 both of which can increase intraocular inflammation and possible risk for
314 CME [21]. Retinectomy is helpful when PVR membranes are not amenable to
315 mechanical peeling, and therefore retinectomy likely indicates severe
316 pathology rather than directly causing CME.

317   Macular detachment was associated with a higher risk of CME, which is
318 in line with prior papers [18]. Of note, previous studies have noted outer
319 nuclear layer CME on OCT of the detached macula [22, 23]. Although the
320 retinal hydration theory, implicated in macular hole edema formation [24],
321 may contribute to post-RRD CME, the presence of leakage on FA suggests
322 dynamic fluid movements as opposed to static, non-leaking cysts. Moreover,
323 absence of SRF after RD repair would theoretically lead to rapid elimination
324 of intraretinal fluid by normal pumping mechanisms. Although such studies

325 for macular detachment and CME development have not been explored [18,

326 25], permanent damage to retinal cellular elements while detached may lead

327 to persistent dysfunction and contribute to CME.

328   There was a significant difference in surgical approaches between

329 groups, with higher rates of combined SB and PPV in aCME eyes. This is not

330 surprising, given that scleral buckles are often combined with PPV for

331 complex or recurrent detachments to support the vitreous base and/or areas

332 of retinal pathology. However, there was significantly more cryotherapy in

333 the nCME group. Cryotherapy at our institution is only used during primary

334 scleral buckling, usually for limited and uncomplicated detachments in

335 phakic patients. While data comparing CME rates between PPV and SB are

336 scant, the correlation between more complicated detachments and CME is

337 consistent [3, 11, 18].

338   After adjusting for the number of surgeries, type of surgery ($P = 0.21$),

339 macular detachment ($P = 0.06$), PVR Grade C ($P = 0.09$) and tamponade

340 type ($P = 0.10$) lost statistical significance. This may be related to the limited

341 sample size, as there remained a trend towards significance. Moreover,

342 these factors are clinically related to the number of surgeries and surgical

343 failure. The interplay of inflammation among these factors requires more

344 formal study.

345   Characteristics of CME on OCT can be useful diagnostic clues, and

346 post-RRD cCME displays distinguishing OCT features (Figure 2). Previous

347 studies have examined OCTs of various conditions associated with CME and

348 noted distinctive findings [13]. These findings could then be used to

349 diagnose conditions accurately as well as account for variability in VA [26].

350 Post-RRD cCME shares features of uveitic CME, such as diffuse macular

351 distribution, inner and outer layer cysts, and absence of hyperreflective foci.

352 This contrasts to post-RRD tCME, which is much less severe, more central

353 and fleeting, and may be a variant of pseudophakic CME.

354   The presence of ERM is common after RRD and may confound CME

355 diagnosis [16]. Although there was a significant difference between groups in

356 the presence of ERM on OCT, there was resolution of CME in only one eye

357 after ERM peeling, suggesting that traction plays a small role in most cases

358 of post-RRD CME. Therefore, there should be high suspicion for post-RRD

359 cCME in any patient status-post RRD repair that has severe, diffuse CME

360 without SRF in the absence of other typical inflammatory or tractional signs.

361   The RPE has a well-studied role in pumping syneretic vitreous fluid

362 through the retina and into the choroidal space [1]. Active fluid transport

363 regulation by the RPE and Muller cells along with maintenance of tight

364 junctional proteins are thought to mitigate CME accumulation [1, 2, 15], and

365 dysfunction of these cells causes an imbalance of fluid inflow and egress.

366 Previous papers examining CME OCT findings note varying SRF rates, from

367 5% in uveitic CME up to 100% in central RVO-associated CME [1, 4, 13, 27].

368 Therefore, the absence of SRF in cCME suggests a grossly functioning RPE

369 and outer retinal barrier.

370   Intravitreal corticosteroids were more effective than intravitreal anti-

371   VEGF or topical medications for cCME in our series. Recent investigations

372   have shown success with intravitreal corticosteroids for chronic post-RRD

373   CME [16, 25]. Thanos et al found favorable responses to DEX all eyes, but in

374   all cases CME recurred after three months. This aligns with pharmacokinetic

375   studies showing a dual-phase response of high dexamethasone

376   concentrations for the first two months after delivery followed by a

377   precipitous decrease during the third month [28]. Experimental studies have

378   demonstrated a reduced half-life of anti-VEGF agents and triamcinolone

379   acetate in vitrectomized eyes compared with non-vitrectomized eyes [28,

380   29], but similar clearances between eyes with DEX. Statistically significance

381   for anatomical improvement was not reached for DEX in our series, likely due

382   to the small number of eyes. Moreover, aphakia has been suggested to

383   cause increased unicameral circulation of inflammatory cytokines [6, 30], but

384   aphakia precludes the use of DEX.   One randomized controlled trial

385   evaluating PPV with SO for RRD with grade C PVR found a significant

386   decrease in CME occurrence at 6 months post-operatively in those with

387   intraoperative DEX [31]. Corticosteroids have been shown to modulate a

388   number of cytokines secreted by retinal cells, such as tumor necrosis factor-

389   α, interleukins-1β, 6, and 8, as well as induce expression of occludin, ZO-1,

390   and claudin-5 [1, 16, 31]. Steroids also modulate expression of aquaporin,

391   predominantly expressed in end-feet of Müller cells and astrocytes.

392   Corticosteroids may therefore stabilize the BRB and encourage resolution of

393 CME, accounting for the increased efficacy of corticosteroids over anti-VEGF

394 agents. Nevertheless, disadvantages of TA and DEX include accelerated

395 cataract formation and risk of increased IOP; however, most patients with

396 cCME will require cataract extraction, and no patient in our series required

397 treatment for ocular hypertension.

398 Average final visit VA was significantly worse in the aCME group even

399 after adjusting for macula-off status and number of surgeries. Reports on

400 recalcitrant CME after PPV for RRD, despite anatomic improvement, found

401 only short-term visual acuity gains [16, 25].

402 Irvine-Gass syndrome (IGS) is another potential diagnosis in these

403 cases. We did not regularly perform FA or optic disc evaluations to check for

404 optic nerve head leakage during the course of follow up. However, IGS is not

405 described after PPV and has been described as a potential treatment option

406 in many cases [32]. Therefore, IGS would have likely responded to topical

407 treatments, steroid injections, or PPV. The OCT appearance of IGS is also less

408 diffuse, more foveocentric, and may be associated with SRF, as opposed to

409 characteristics noted with post-RRD cCME.

410 Our paper has a relatively large sample size of post-RRD CME, long-

411 term patient records and follow up, and variety of treatments. Despite this,

412 our study has several limitations. The retrospective analysis precluded

413 standardized imaging and treatment protocols. Significant loss to follow-up

414 likely led to underreporting of chronic post-RRD CME and an inability to

415   accurately determine incidence. The high percentage of CME likely relates to

416   inclusion of eyes that had initial RRD repairs prior to the inclusion period and

417   multiple referrals for complex cases. We were unable to determine after

418   which surgery CME appeared due to inconsistent timing and absence of OCT

419   acquisition between surgeries, or missing outside records. A small number of

420   eyes received anti-VEGF injections, and greater numbers may show CME

421   improvement. A larger, prospective study evaluating complex macular

422   surgeries is warranted.

423   In conclusion, cCME after RRD is a complex entity with interconnected

424   risk factors. A high index of suspicion based on risk factor and imaging

425   characteristics can allow anticipation of cCME development and early

426   treatment. Currently, corticosteroids have the most evidence of treatment

427   success, and prompt intervention may provide better functional and

428   structural outcomes.

429

430   **LIST OF ABBREVIATIONS**

431   CME = cystoid macular edema, tCME = transient CME, cCME = chronic CME,

432   aCME = all CME

433   DR = diabetic retinopathy

434   AMD = age-related macular degeneration

435   RVO = retinal vein occlusion

436   RP = retinitis pigmentosa

437   RRD = rhegmatogenous retinal detachment

438   FA = fluorescein angiography

439   OCT = optical coherence tomography

440   SB = scleral buckle

441   PPV = pars plana vitrectomy

442   VEGF = vascular endothelial growth factor

443   EHR = electronic health records

444   CPT = current procedural terminology

445   TA = triamcinolone acetonide

446   DEX = dexamethasone intravitreal implant

447   CST = central subfield thickness

448   ETDRS = early treatment for diabetic retinopathy study

449   SD = standard deviation

450   PVR = proliferative vitreoretinopathy

451   PFCL = perfluorocarbon liquid

452   INL = inner nuclear layer

453   OPL = outer plexiform layer

454   EZ = ellipsoid zone

455   ELM = external limiting membrane

456   ERM = epiretinal membrane

457   RPE = retinal pigment epithelium

458   SRF = subretinal fluid

459   NSAID = non-steroidal anti-inflammatory drug

460   IOP = intraocular pressure

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461   SO = silicone oil

461   SO = silicone oil

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Declarations

Ethics Approval and consent to participate: This research study was conducted retrospectively from data obtained for clinical purposes. An IRB official waiver of ethical approval was granted from the IRB of the University of California Los Angeles Office of Human Research Protection (IRB#16-000574).

Consent for publication: Not applicable

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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	aCME	nCME	P value	[1]Adjusted P value
Demographic Data				
Number of eyes	25 (25%)	74 (75%)		
Follow-up (months)	21.4 ± 12.1	20.4 ± 10.8	0.87	
Sex, Female	8 (32%)	38 (34%)	0.09	
Age (years)	64.1 ± 11.6	56.7 ± 18.0	0.09	
Clinical Data				
Right eye	11 (44%)	40 (54%)	0.38	
Glaucoma	4 (16%)	6 (8%)	0.26	
Lens status			< 0.001	0.008
Phakic	1 (4%)	44 (60%)		
Pseudophakic	14 (56%)	28 (38%)		
Aphakic	10 (40%)	2 (3%)		
Macula off[a]	20/24 (83%)	31/70 (44%)	0.001	0.06
PVR Stage C[a]	15/24 (63%)	5/74 (7%)	< 0.001	0.09
Final VA (LogMAR)	0.85 ± 0.80	0.20 ± 0.30	< 0.001	[b]0.012
ERM	18 (72%)	28 (38%)	0.005	
Surgical details				
Number of surgeries	3.5 ± 1.8	1.4 ± 0.9	< 0.001	
Multiple PPV	21 (84%)	17 (23%)	< 0.001	[c]—
Referred after surgery elsewhere	12 (48%)	5 (7%)	< 0.001	0.31
Number of surgery outside	1 ± 1.3	0.095 ± 0.4	< 0.001	
Type of surgery			< 0.001	0.21
SB	*1 (4%)*	*25 (34%)*		
PPV	*7 (28%)*	*28 (38%)*		
PPV+SB	*17 (68%)*	*21 (28%)*		
Tamponade agent			< 0.001	0.10
None/Air	*1 (4%)*	*24 (32%)*		
Gas (SF$_6$ or C$_3$F$_8$)	*8 (32%)*	*46 (62%)*		
Silicone Oil	*16 (64%)*	*4 (5%)*		
Cryotherapy[a]	4/24 (17%)	30/73 (41%)	0.047	0.036
Retinectomy	9 (36%)	4 (5%)	< 0.001	0.009
PFCL[a]	18/23 (78%)	35/47 (75%)	0.73	0.38

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589 aCME: all (chronic + transient) cystoid macular edema; nCME: no cystoid macular
590 edema; PVR: proliferative vitreoretinopathy; VA: visual acuity; LogMAR: (logarithm
591 of the minimum angle of resolution); PPV: pars-plana vitrectomy; ERM: epiretinal
592 membrane; SB: scleral buckle; PFCL: perfluorocarbon liquid
593 [a]Denominators are provided if the number is less than the total number of eyes in
594 the category due to missing or incomplete data
595 [b]Final VA adjusted P value from a model with covariates for total number of
596 surgeries and Macula on/off.
597 [c]Adjusted model not possible due to collinearity of Multiple PPV with number of
598 surgeries (i.e. those with Multiple PPV had greater than 2 surgeries, while those with
599 no PPV had fewer).
600 [1]P-value for difference after adjustment for total number of surgeries.
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602 _____

603 Table 1 should be placed at an area near the Risk Factors section of results

604 for viewing by the reader.

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606

607 **Fig. 1** Flowchart of patient selection process. ICD-9: International

608 Classification of Disease, 9th edition. CPT: Current Procedural Terminology.

609 CME: Cystoid Macular Edema.

610

611 **Fig. 2** Spectral-domain optical coherence tomography and infrared image

612 elevation overlays of two different patients with chronic cystoid macular

613 edema post-rhegmatogenous retinal detachment. The scan in Row A

614 demonstrates schisis-like changes. The scan in Row B demonstrates

615 confluent cystic cavities spanning retinal layers that developed over two

616 years. In both scans, note diffuse, asymmetric distribution of retinal cysts

617 crossing the horizontal raphe, involvement of inner and outer retinal layers,

618   absence of subretinal fluid, and relative preservation of outer retinal bands

619   subjacent to retinal edema.

620

621   **Fig. 3** Spectral-domain optical coherence tomography (OCT) images of

622   chronic cystoid macular edema (CME) post-rhegmatogenous retinal

623   detachment (RRD) repair of the left eye, with dates and visual acuities (VA).

624   Panel A: OCT prior to dexamethasone implant (DEX) injection. Panel B: OCT

625   one month after DEX injection, showing resolution of CME but retinal layer

626   atrophy. Modest VA improvement was noted. Panel C: OCT four months after

627   injection, showing recurrence of CME in a similar distribution and slight

628   decrease in VA.

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632   **ADDITIONAL FILES**

633   File name: Table S1

634   Format: .docx

635   Title: Supplemental Table 1

636   Description: descriptive statistics for all three groups, as explained in Results

637   population section