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ORIGINAL RESEARCH

Epiretinal membrane and cystoid macular edema as predictive factors of recurrent proliferative vitreoretinopathy

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Purpose: Proliferative vitreoretinopathy (PVR) is the most common cause of recurrent retinal detachment (RD). We sought to determine the predictive factors of recurrent PVR formation and the need for additional vitreoretinal surgical intervention after uncomplicated primary RD repair.

Methods: This is a retrospective single-center case–control study of consecutive patients with PVR formation after uncomplicated RD repair. Logistic regression was used to assess factors associated with recurrent PVR formation.

Results: Thirty-seven eyes (37 patients) who had recurrent RD secondary to PVR formation were included. Among those, 27 eyes needed one additional surgery, whereas the remainder 10 eyes required two or more additional surgeries. In the univariate analysis, patients who had cystoid macular edema (CME) after the second surgery were 8.33 times (crude odds ratio [COR], 95% confidence interval [CI]: 1.23–56.67, p=0.0302) more likely to have recurrent PVR formation compared to those who did not have CME after the second surgery. Similarly, those who had epiretinal membrane (ERM) after the second surgery were 8.00 times (COR, 95% CI: 1.43–44.92, p=0.0182) more likely to have recurrent PVR formation compared to those who did not have ERM after the second surgery. In the multivariate analysis, patients who had ERM after the second surgery were 8.20 times (adjusted odds ratio [AOR], 95% CI: 1.08–62.40, p=0.0422) more likely to develop recurrent PVR compared to those who did not have ERM after the second surgery, when adjusted for age, sex, and CME after the second surgery.

Conclusion: ERM and CME are potential predictive factors for recurrent PVR formation after uncomplicated primary RD repair. Early recognition and treatment of ERM and CME may be critical to prevent subsequent PVR formation and improve visual outcomes.

Keywords: epiretinal membrane, cystoid macular edema, proliferative vitreoretinopathy, retinal detachment, rhegmatogenous retinal detachment

Introduction

Proliferative vitreoretinopathy (PVR) is characterized by the formation of epiretinal and subretinal contracting membranes, and it is the most common reason for surgical failure following rhegmatogenous retinal detachment (RD).[1,2] PVR formation occurs in ~5%–10% of all RDs.[3,4] The pathophysiology of PVR formation involves cellular proliferation, migration, and inflammation.[5,6]

Our previous study suggested that cigarette smoking, RD involving the macula, and large-gauge vitrectomy are significant risk factors predictive of PVR formation after uncomplicated primary RD repair (Xu K et al, unpublished data, 2017). At the onset of PVR formation, some patients will have successful repair with one additional surgery;

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however, recurrent PVR requiring multiple surgeries remain some of the most challenging cases for retina surgeons today. Currently, the clinical findings associated with recurrent PVR formation represent a knowledge gap in the literature. In our study, we identify the predictive clinical findings associated with recurrent PVR formation and the need for additional vitreoretinal surgical intervention.

Methods

Study design

This is a retrospective case–control study involving consecutive RD patients who required subsequent retina surgery due to postoperative recurrent RD secondary to PVR formation. Those patients were evaluated and treated at a multi-site single private practice institution (VitreoRetinal Surgery, PA, Minneapolis, MN, USA) involving nine different US-trained vitreoretinal surgeons between January 2014 and December 2015. This study adheres to the tenets of the Declaration of Helsinki, and it was approved by the Salus Institutional Review Board (Austin, TX, USA). All patients provided written consent to review their medical records.

Patient charts and operative reports were carefully reviewed. All patients had required routine preoperative and postoperative examinations. For each patient, a detailed fundus drawings were documented in the clinical and surgical notes which included the number and location of retinal tears as well as any findings of PVR. PVR was graded according to the Silicone Study Group classification.[7] Specifically, PVR cases were defined as having proliferative epiretinal membrane (ERM) formation (eg, ERMs and starfolds), with or without subretinal membranes, causing diffuse contraction of the posterior retina resulting in retinal re-detachment and need for additional surgery. When ERM was identified after primary RD repair, ERM and internal limiting membrane peels were done at the time of recurrent RD repair (second surgery).

Inclusion and exclusion criteria

All patients who underwent uncomplicated RD repair without preoperative PVR formation were identified. After PVR formation, patients who needed one or more additional surgeries due to PVR formation after uncomplicated primary RD repair were included. Any patient with a past history of recurrent RD (repaired elsewhere), a past vitreoretinal surgery for any cause (eg, macular hole or ERM surgery), or a diagnosis of complicated RD on presentation (eg, RD with PVR at initial presentation, tractional RD, RD caused by a giant retinal tear, or RD secondary to trauma or penetrating injury) was excluded. Additionally, any patients with vision loss secondary to other comorbid eye conditions other than rhegmatogenous RD upon initial repair (such as glaucoma, ERM, and macular edema) were excluded. Patients who experienced an intraoperative complication during primary RD repair (eg, vitreous hemorrhage and suprachoroidal hemorrhage) were also excluded.

Identification of cases and controls

Included patients were divided into either the recurrent PVR group (PVR formation requiring two or more additional surgeries) or the control group (PVR formation was repaired with only one additional surgery). In addition to clinical examinations, intravenous fluorescein angiography and spectral domain-optical coherence tomography (SD-OCT) were used to identify the presence of CME while SD-OCT was used to detect the ERM.

Potential predictive variables for recurrent PVR formation

Preoperative variables included age, sex, cigarette smoking status, alcohol intake, preoperative best-corrected visual acuity (BCVA) via logarithm of the minimum angle of resolution (LogMAR) acuity, intraocular pressure (IOP), high myopia (defined as refractive error ≥ -6.0 D),[8] family history of RD, lens status (phakia versus pseudophakia), location of RTs, total number of RTs, large RT ($>30°$ but $<90°$), RD involving macula, presence of lattice degeneration, presence of cystoid macular edema (CME), presence of ERM, presence of vitreous hemorrhage, duration of RD symptoms (eg, photopsias, floaters, or peripheral vision loss; defined as the time between initial RD symptoms and primary surgery for RD repair).

Intraoperative variables included surgical technique (primary scleral buckle [SB], pars plana vitrectomy [PPV], or combination of SB with vitrectomy), PPV gauge (20, 23, or 25 gauge), and tamponade agent (sulfur hexafluoride [SF_6] gas, perfluoropropane [C_3F_8] gas, or silicone oil [SO]).

Postoperative factors included the formation of PVR after the primary surgery, postoperative CME, postoperative ERM, total number of surgeries needed for anatomical success, follow-up time, final postoperative BCVA, and final postoperative IOP.

Statistical analysis

Descriptive analysis was used to describe the sample characteristics. Continuous variables were described in means and standard deviations (SDs). Categorical variables were

described in frequencies and percentages (%). To compare different groups in categorical variables, chi-square tests or Fisher's exact tests (n<5) were used. Student's *t*-tests were used to compare the means for different categories.

Logistic regression analysis was used to assess the potential factors associated with recurrent PVR formation after uncomplicated primary RD repair. For univariate analysis, each preoperative, intraoperative, or postoperative factor was considered separately in a model to predict the recurrent PVR formation after an uncomplicated primary RD repair. Crude odds ratio (COR) and 95% confidence interval (CI) were obtained for each factor. Multivariate logistic regression models were used to identify the possible risk factors for recurrent PVR formation after uncomplicated primary RD repair. Adjusted odds ratio (AOR) and 95% CI were obtained for each factor in the multivariate analysis. Factor with a two-tailed *p*-value <0.05 was considered significant. All statistical analyses were performed using the SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Thirty-seven eyes (37 patients) that had PVR formation following uncomplicated primary surgery for RD repair were included. During the study period, there were 2,760 patients who had surgery for primary RD repair and all of them had a minimal 1-year follow-up after the surgery. Among those patients, 37 (1.3%) developed PVR. As reported in our previous study, surgeon factor was not associated with PVR formation after primary RD repair (Xu K et al, unpublished data, 2017).

Among those, 27 eyes required one additional surgery, whereas 10 eyes required two or more additional surgeries. The mean age of the study sample was 63.7 (SD =12.1) years and 54.1% patients were male (n=20). Overall, the mean duration of preoperative RD symptoms was 18.5 (SD =26.1) days, and the mean follow-up time was 368.0 (SD =166.8) days. The mean BCVA for all patients at the final follow-up was 1.0 LogMAR (SD =0.7). The mean BCVA at final follow-up was 1.3 LogMAR (SD =0.7) for recurrent PVR group and 0.9 LogMAR (SD =0.7) for control group. The preoperative and postoperative characteristics between recurrent PVR group and control group are shown in Table 1.

Most patients had either combination of SB plus PPV (n=23, 62.3%) or PPV alone (n=13, 35.0%) as the primary surgery for uncomplicated RD repair. SF_6 gas (n=23, 62.2%) was the most commonly use tamponade agent in comparison with C_3F_8 gas (n=12, 32.4%) for the primary repair. 20-, 23-, and 25-gauge vitrectomy was performed in 8 (22.2%), 19 (52.8%), and 9 (25.0%) patients, respectively. Table 2 shows the surgical details comparing the recurrent PVR and control groups.

Table 1 Baseline sample characteristics (n=37)

Characteristics	Control group (n=27)		Recurrent PVR group (n=10)	
	Mean (SD)	Frequency (%)	Mean (SD)	Frequency (%)
Preoperative factors				
Age (years)	63.3 (13.7)		64.8 (6.6)	
Sex				
Male		16 (59.3)		4 (40.0)
Duration of RD symptoms (days)				
≤14		15 (55.6)		8 (80.0)
>14		12 (44.4)		2 (20.0)
High myopia				
Yes		9 (33.3)		6 (60.0)
No		18 (66.7)		4 (40.0)
RD involving macula				
Yes		17 (63.0)		5 (50.0)
No		10 (37.0)		5 (50.0)
Postoperative factors				
BCVA (LogMAR) at the last visit	0.9 (0.7)		1.3 (0.7)	
>0.4		5 (18.5)		0 (0.0)
≤0.4		22 (81.5)		10 (100.0)
Final IOP (mmHg)	15.1 (3.9)		14.3 (8.9)	
Follow-up (days)	386.3 (170.1)		318.5 (154.8)	
Successful anatomical repair at the last visit				
Yes		100 (100)		100 (100)
No		0 (0.0)		0 (0.0)

Abbreviations: SD, standard deviation; PVR, proliferative vitreoretinopahty; RD, retinal detachment; BCVA, best-corrected visual acuity; IOP, intraocular pressure.

Table 2 Surgical details for the primary and the secondary surgeries for recurrent PVR and control groups

Details	Control group (n=27)		Recurrent PVR group (n=10)	
	Primary surgery, n (%)	Secondary surgery, n (%)	Primary surgery, n (%)	Secondary surgery, n (%)
Surgical technique				
Scleral buckle	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pars plana vitrectomy	8 (29.6)	16 (59.3)	5 (50.0)	6 (60.0)
Scleral buckle plus pars plana vitrectomy	18 (66.7)	11 (40.7)	5 (50.0)	4 (40.0)
Tamponade agent				
Sulfur hexafluoride (SF_6)	17 (63.0)	4 (14.8)	6 (60.0)	0 (0.0)
Octafluoropropane (C_3F_8)	8 (29.6)	5 (18.5)	4 (40.0)	4 (40.0)
Silicon oil	2 (7.4)	18 (66.7)	0 (0.0)	6 (60.0)
Pars plana vitrectomy gauge (g)				
20	6 (22.2)	5 (18.5)	2 (20.0)	1 (10.0)
23	14 (51.9)	18 (66.7)	6 (60.0)	7 (70.0)
25	7 (25.9)	4 (14.8)	2 (20.0)	2 (20.0)

Abbreviation: PVR, proliferative vitreoretinopathy.

There was no difference in the percentage of postoperative CME and postoperative ERM after the primary surgery for uncomplicated RD repair between recurrent PVR group and control group (Table 3). However, a significant higher percentage of patients had CME and ERM after the second surgery in the recurrent PVR group compared to control group (Table 3).

In the univariate analysis (Table 4), patients who had CME after the second surgery were 8.33 times (COR, 95% CI: 1.23–56.67, p=0.0302) more likely to have recurrent PVR formation compared to those who did not have CME after the second surgery. Similarly, those who had ERM after the second surgery were 8.00 times (COR, 95% CI: 1.43–44.92, p=0.0182) more likely to have recurrent PVR formation compared to those who did not have ERM after the second surgery. Preoperative and intraoperative factors were not found to be associated with recurrent PVR formation (Table 4). In the multivariate analysis (Table 5), patients who had ERM after the second surgery were 8.20 times (AOR, 95% CI: 1.08–62.40, p=0.0422) more likely to develop recurrent PVR compared to those who did not have ERM after the second surgery, when adjusted for age, sex, and CME after the second surgery.

Discussion

PVR represents an anomalous scarring process after surgery due to inflammation and cellular proliferation. It is a frequent complication of RD and vitreoretinal surgery, causing the formation of preretinal avascular fibrocellular membranes.[9] Despite the evolution of vitreoretinal surgical techniques, the frequency of PVR remained largely unchanged.[10] In our study, we found that the presence of ERM and CME might be predictive of recurrent PVR formation after uncomplicated primary RD repair.

ERMs consist of various cell types including retinal pigment epithelial cells, fibroblasts, glial cells, and vascular endothelial cells; however, the exact mechanism for ERM formation is not clear.[11] ERMs have been reported to be associated with PVR.[12] Studies showed that ERMs formed after surgery for complicated RD with PVR.[13,14] It was suggested that there was a significant association between clinical grades of PVR and the expression levels of specific

Table 3 Complications after the primary and the secondary surgeries

Postoperative complications	Postprimary surgery		p-value	Postsecondary surgery		p-value
	Control group, n (%)	Recurrent PVR group, n (%)		Control group, n (%)	Recurrent PVR group, n (%)	
Cystic macular edema	1 (3.7)	3 (30.0)	0.0522	2 (7.4)	4 (40.0)	0.0347
High intraocular pressure	0 (0.0)	1 (10.0)	0.2703	0 (0.0)	0 (0.0)	
Hypotony	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Vitreous hemorrhage	0 (0.0)	0 (0.0)		1 (3.7)	0 (0.0)	0.7297
Keratopathy	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Epiretinal membrane	10 (37.0)	2 (20.0)	0.4447	3 (11.1)	5 (50.0)	0.0191

Abbreviation: PVR, proliferative vitreoretinopathy.

Table 4 Univariate analysis: factors associated with recurrent PVR formation after the primary surgery for retinal detachment repair (n=37)

Variables	COR	*p*-value
Preoperative factors		
Age (years)		
>55	2.05 (0.21, 20.05)	0.5389
≤55	1.00	
Sex		
Female	2.18 (0.50, 9.58)	0.3015
Male	1.00	
Cigarette smoking status		
Previous or current	2.51 (0.53, 11.83)	0.2436
Never	1.00	
Alcohol intake status		
Previous or current alcohol intake	1.03 (0.24, 4.53)	0.9695
Never	1.00	
Duration of RD symptoms (days)		
>14	3.20 (0.57, 17.97)	0.1864
≤14	1.00	
High myopia		
Yes	3.00 (0.67, 13.40)	0.1503
No	1.00	
RD involving macula		
Yes	0.59 (0.14, 2.55)	0.4778
No	1.00	
Location of retinal break(s)		
Inferior 180° ± superior 180°	0.73 (0.15, 3.47)	0.6911
Superior 180°	1.00	
Number of retinal break(s)		
1	2.35 (0.42, 13.34)	0.3338
≥2	1.00	
Lens status		
Phakic	1.25 (0.29, 5.35)	0.7635
Pseudophakic	1.00	
Lattice degeneration of operated eye		
Yes	3.79 (0.41, 35.05)	0.2406
No	1.00	
Lattice degeneration of contralateral eye		
Yes	2.05 (0.21, 20.05)	0.5389
No	1.00	
Large tear		
Yes	3.13 (0.38, 25.92)	0.2911
No	1.00	
Vitreous hemorrhage		
Yes	5.35 (0.74, 38.64)	0.0959
No	1.00	
BCVA (LogMAR)		
>0.4	1.20 (0.27, 5.25)	0.8086
≤0.4	1.00	
IOP (mmHg)		
>15	1.58 (0.35, 7.17)	0.5511
≤15	1.00	
Intraoperative factors		
Surgical technique		
Pars plana vitrectomy	2.38 (0.54, 10.53)	0.2551
Scleral buckle ± pars plana vitrectomy	1.00	
Tamponade agent	n/a	n/a
Octafluoropropane (C_3F_8)		
Sulfur hexafluoride (SF_6)		
Pars plana vitrectomy gauge (g)		
20 or 23	1.40 (0.24, 8.24)	0.7099
25	1.00	
Postprimary surgery		
Cystic macular edema		
Yes	1.89 (0.36, 9.97)	0.4551
No	1.00	
Epiretinal membrane		
Yes	2.35 (0.42, 13.34)	0.3338
No	1.00	
Postsecondary surgery		
Cystic macular edema		
Yes	8.33 (1.23, 56.67)	0.0302
No	1.00	
Epiretinal membrane		
Yes	8.00 (1.43, 44.92)	0.0182
No	1.00	

Abbreviations: PVR, proliferative vitreoretinopathy; COR, crude odds ratio; RD, retinal detachment.

cytokines and/or growth factors in the vitreous fluid.[11] Interestingly, expression of these factors and their receptors are also found in ERMs.[11] In our study, we found that the development of ERMs was associated with recurrent PVR formation. This might suggest that ERM is a surrogate for uncontrolled underlying PVR. In our opinion, early ERM formation in the context of a history of PVR might suggest careful consideration for removal because this is associated with a high rate of progression to PVR development. We postulate that ERM formation in the context of PVR might be due to an increase in cytokines and growth factors

Table 5 Multivariate analysis: factors associated with recurrent PVR formation after the primary surgery for retinal detachment repair (n=37)

Variables	AOR	*p*-value
Preoperative factors		
Age (years)		
>55	2.58 (0.16, 41.96)	0.0506
≤55	1.00	
Sex		
Female	2.74 (0.42, 17.73)	0.2905
Male	1.00	
Postsecondary surgery		
Cystic macular edema		
Yes	5.13 (0.59, 44.40)	0.1372
No	1.00	
Epiretinal membrane		
Yes	8.20 (1.08, 62.40)	0.0422
No	1.00	

Abbreviations: PVR, proliferative vitreoretinopathy; AOR, adjusted odds ratio.

that continue to drive PVR formation, retinal foreshortening, and subsequent RD.

CME frequently develops as a result of blood–retinal barrier dysfunction.[15] It has been suggested that inflammatory mediators probably initiate the development of inflammatory macular edema, but the exact factors and events responsible for further CME development have not yet been identified.[16] Kiss et al showed that CME can occur after SO removal for complicated RD with PVR repair.[13] Similarly, CME was also reported after PPV and gas tamponade for rhegmatogenous RD complicated by PVR.[14] In our study, the development of postoperative CME was associated with recurrent PVR formation in the univariate analysis. This might indicate that CME could be an early sign for PVR formation after uncomplicated primary RD repair. However, this association was not found in the multivariate analysis, which might be due to the small sample size and associated low statistical power.

CME in cases of PVR can be difficult to treat. From our data, we can surmise that CME following recurrent PVR likely represents a derangement of inflammatory mediators that accelerate the progression of PVR formation and increase rates of RD. In both the cases of ERM and CME formation in PVR, we can see that these may be aberrant processes linked to local inflammatory disruption and should be considered for early and aggressive treatment.

Our study has some limitations, including its retrospective nature and small sample size. Studies with larger sample sizes are necessary to further assess the predictive factors for recurrent PVR formation in the context of uncomplicated primary RD repair. In addition, basic science research will be important and helpful to unveil the association between ERM, CME, and PVR formation among patients with uncomplicated primary RD repair.

Conclusion

To our knowledge, this is the first study to assess the predictive factors for recurrent PVR formation after uncomplicated primary RD repair. In this study, we identify ERM and CME as potential predictive factors for recurrent PVR formation after uncomplicated primary RD repair. This suggests that early recognition and treatment of ERM and CME might be important to prevent PVR formation and to achieve better visual outcome for those who undergo uncomplicated primary RD repair.

Disclosure

The authors report no conflicts of interest in this work.

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