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Proliferative Vitreoretinopathy: A Review

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Abstract

Proliferative vitreoretinopathy (PVR) is the most common cause for failure of rhegmatogenous retinal detachment repair and is characterized by the growth and contraction of cellular membranes within the vitreous cavity and on both sides of the retinal surface as well as intraretinal fibrosis. Currently, PVR is thought to be an abnormal wound healing response that is primarily driven by inflammatory, retinal, and RPE cells. At this time, surgery is the only management option for PVR as there is no proven pharmacologic agent for the treatment or prevention of PVR. Laboratory research to better understand PVR pathophysiology and clinical trials of various agents to prevent PVR formation are ongoing.

Introduction

Proliferative vitreoretinopathy (PVR) is the most common cause for failure of rhegmatogenous retinal detachment repair and is characterized by the growth and contraction of cellular membranes within the vitreous cavity and on both sides of the retinal surface as well as intraretinal fibrosis (Figure 1).^{1,2} Contraction of these membranes can cause the retina to redetach and transform a rhegmatogenous detachment into a tractional detachment.³ Intraretinal fibrosis can prevent the retina from flattening even after removal of all membranes. The incidence of PVR in all cases of retinal detachment is estimated to be 5–10%.^{4,5} The incidence of PVR has largely remained unchanged in prospective studies despite the evolution of vitreoretinal techniques over the past 25 years, including valved trocars and smaller gauge instrumentation.^{6–9}

Approximately 77% of postoperative forms of PVR appear within one month after retinal detachment surgery and 95% appear within 45 days.^{2,4} Following PVR detachment surgery, the anatomic success rate has been reported to be 45–85%.^{10–15} The final functional success rates of PVR detachment surgery were 26–67%, with functional success defined by most studies as a final visual acuity of 5/200 or better.^{10,16–18}

Numerous risk factors for the development of PVR have been identified. Almost all risk factors for PVR are associated with intravitreal dispersion of retinal pigment epithelial cells or breakdown of the blood-ocular barrier, which are prerequisite to the development of PVR.

¹ Preoperative risk factors include prolonged intraocular inflammation, prior infectious retinitis, lower intraocular pressure secondary to intraocular inflammation, vitreous hemorrhage, aphakia, prior intraocular surgery, choroidal detachment, retinal breaks greater than one clock hour, larger number of breaks, larger extent of retinal detachment, and preoperative grade A or B PVR.^{4,19–26} Intraoperative risk factors for PVR development include vitreous or subretinal hemorrhage, inability to completely seal a retinal tear, intraoperative choroidal detachment, pigment release during endodrainage, excessive cryotherapy and endolaser, and vitreous loss during external subretinal fluid drainage.^{4,24,26–29} Postoperative risk factors for inducing PVR formation include prolonged inflammation or uveitis, intraocular hemorrhage after surgery, choroidal detachment, use of air or sulfur hexafluoride (SF₆) or air, multiple surgical procedures, and persistent traction on retinal breaks.^{1,2,19,26,27,30} The only identified modifiable risk factor associated with PVR is cigarette smoking.³¹

Proliferative Vitreoretinopathy Grading

The first widely recognized classification system for PVR was published by The Retina Society Terminology Committee in 1983 (Table 1). Grade A PVR was defined as the presence of vitreous haze and pigment clumps.³ Grade B PVR included the presence of surface retinal wrinkling and/or rolled edges of the retinal break with possible retinal stiffness and vessel tortuosity.³ Grade C PVR was defined as the presence of full thickness retinal folds in one (C-1), two (C-2), or three (C-3) quadrants.³ Grade D was defined as fixed retinal folds in four quadrants resulting in a wide funnel shape (D-1), narrow funnel shape (D-2), or closed funnel without a view of the optic disc (D-3).³

One of the major shortcomings of this classification scheme is the lack of differentiation between anterior and posterior PVR. In order to address this, the Silicone Study recommended a new classification scheme (Table 1): Grades A and B remained the same, but Grades C and D were replaced with Grades P (posterior form) and A (anterior form).³² Grades P and A were further defined by the types of contraction and the extent of PVR was measured by the number of clock hours involved.³²

The Retina Society Terminology Committee updated its classification scheme in 1991 (Table 1).³³ The new scheme describes three grades of increasing severity and emphasized the anterior and posterior locations of proliferation. Grades A and B remained the same. Grade C was modified to include a more detailed description of the location of proliferation, types of contraction, and extent in clock hours. Additionally, Grade D was eliminated. Grade C was defined as a full-thickness retinal folds and/or subretinal bands and pathologic changes that could be posterior, anterior, or both. Posterior grade C PVR was divided into focal contractions resulting in starfold membrane formation (Type 1) and/or diffuse contractions resulting from confluent starfolds that can result in a closed funnel configuration (Type 2). Grade C PVR included anterior or posterior subretinal bands (Type 3). Anterior grade C was divided into circumferential contraction (Type 4) along the posterior margin of the vitreous base and anterior displacement (Type 5) or the peripheral retina.³³ However, due to the complexity of this grading scheme, it has rarely been incorporated into clinical practice.

Additionally, each of the different grading schemes are used in clinical studies and approximately 25% of PVR studies do not use or identify a grading scheme.³⁴

Pathophysiology

PVR is a multifactorial process that is a result of scarring, the end stage of wound healing, after retinal detachment (Figure 2).² When a rhegmatogenous retinal detachment occurs, two primary events occur that act as the initiating factors of the potential PVR cascade. These events are the breakdown of the blood-retinal barriers and retinal hypoxia.^{1,4,35} The alteration of the interface between the outer retina and the retinal pigment epithelium (RPE) can result in the migration of the RPE cells into the vitreous cavity and onto the retina surface, and migration of retinal cells (e.g. glial cells) through the retina onto its surface.

When the blood-retinal barrier is disrupted, this leads to an increase in the chemotactic and mitogenic activity in the vitreous cavity.³⁶ This occurs secondary to the influx of both cytokines and growth factors from the systemic circulation and influx of systemic circulation inflammatory cells that interact with hyalocytes, various retinal cells (e.g. glial cells), and retinal pigment epithelial (RPE) cells to drive further local production of cytokines and growth factors in the vitreous cavity.

Multiple inflammatory cells have been identified in the vitreous fluid and epiretinal membranes of PVR patients, including macrophages, CD4+ and CD8+ T lymphocytes, B lymphocytes, major histocompatibility (MHC) class II positive cells.^{37,38,39–41} Deposits of immunoglobulins and complement have also been found in PVR epiretinal membranes and vitreous fluid.^{37,42} Intracellular adhesion molecule 1 (ICAM-1) and lymphocyte function-associated antigen 1 (LFA-1), which mediate the interaction of leukocytes with other cells and the extracellular matrices, have also been found in PVR membranes.⁴³

Growth factors and cytokines/chemokines enter the vitreous cavity through the impaired blood retina barrier and through interaction between the immune cells and local cells of the retina and vitreous. Some of the most important among them are platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), granulocyte-colony stimulating factor (G-CSF), acidic and basic fibroblastic growth factor (aFGF and bFGF), insulin-like growth factor 1 (IGF-1), connective tissue growth factor (CTGF), transforming growth factor α (TGF- α), transforming growth factor β (TGF- β), tumor necrosis factor α (TNF- α), interferon β (IFN- β), interferon γ (INF γ), interleukin 1 (IL-1), interleukin 1 β (IL-1 β), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 10 (IL-10), and chemokines such as C-C motif chemokine ligand 3, 4, and 5 (CCL3, CCL4, and CCL5).^{44–55} Several of these growth factors and cytokines have been implicated in the stimulation of RPE and glial cells.^{56–58,44} The presence and concentration of growth factors, cytokines, and chemokines may be biomarkers for predicting development and severity of PVR.^{45,59–61}

TGF- β is a cytokine that regulates the differentiation, migration, apoptosis, and immune function of cells as well as the synthesis of the extracellular matrix. It has been found in high concentrations in the vitreous of patients with PVR.⁶² Quantities of TGF- β 2 were found to be directly proportional to the extent of fibrosis.⁶³ PDGF is a growth factor that functions in

intercellular interaction between retinal cells.⁶⁴ Studies have shown that PDGF receptor α (PDGFR- α) is activated in higher proportion in eyes with PVR. Direct activation of PDGFR- α by PDGF leads to rapid clearance of the receptor from the cell surface with subsequent degradation. Non-PDGFs, such as VEGF, bFGF, EGF, insulin, and HGF, can also function to indirectly activate the PDGFR- α receptor by inducing tyrosine phosphorylation of PDGFR- α . Indirect activation of the PDGFR- α by non-PDGFs promotes persistent receptor signaling and induces prolonged activation of phosphatidylinositol 3-kinase (PI3K)/Akt, activating murine double minute (MDM2) to suppress p53 levels, and drive processes involved in PVR-survival, proliferation, and contraction.^{65,66}

Many studies of epiretinal membranes in PVR have identified fibroblast or fibrocyte cells.⁶⁷ Some have argued that these cells represent transformed RPE cells or originate from vascular endothelial cells, glial cells, macrophages, or hyalocytes.^{38,68–70} Based upon the finding of fibroblastic cells with cytoplasmic monofilaments, it has been proposed that membrane shortening is mediated by the intrinsic contraction of these cells, leading to the tractional forces responsible for the clinical features of PVR. Another study suggested an alternate mechanism of membrane contraction in which collagen fibers are pulled by the RPE cells, alternating the extension and retraction of their lamellipodia.⁷⁰ Through either mechanism, the contraction can result in additional retinal breaks and redetachment of the retina.⁴

After separation of the retina in a retinal detachment, the retinal outer layers become ischemic and the photoreceptors undergo cell death.⁷¹ While there are several pathways for cell death, apoptosis is the principal mechanism of photoreceptor loss after a retinal detachment.^{72,73} Apoptosis has two major signaling cascades, the extrinsic and intrinsic pathways, which lead to DNA fragmentation and cell death. Both pathways involve caspases.^{74–76} The initiation of photoreceptor apoptosis involves the release of cytokines from stressed and damaged tissues. The cytokines have chemotactic properties, which can attract and activate macrophages, Mueller cells, astrocytes, and microglia.^{51,54,59,77–82} The activation of these cells lead to oxidative stress that could contribute to further cytotoxic effect on the photoreceptors after a retinal detachment.⁷⁷ Additionally, retinal detachment was found to induce the proliferation of non-neuronal cells, such as astrocytes, endothelial cells, pericytes, and microglia, peaking at 3–4 days after retinal detachment.⁸³ Reattachment of the retina can reverse some of these changes, including proliferation of endothelial cells and pericytes, especially if performed within one day.⁸⁴ Cell death pathways may influence the development of intraretinal fibrosis in PVR.

The role of genetics in PVR development has been studied by the Retina 4 Project using a candidate gene association study. Two pro-fibrotic genes, SMAD7 and the TNF locus and two genes involved in apoptosis, p53 and MDM2, have been implicated in the formation of PVR through this study. The identification of both fibrotic and apoptotic genes further supports the theory that both of these pathologic processes play a key role in the development of PVR.

Pharmacologic prevention and treatment of PVR

At this time there is no proven pharmacologic agent for the treatment or prevention of PVR. Pharmacologic interventions have mostly targeted inflammation, cell proliferation, and fibrosis.² Corticosteroids were the first drugs tested for PVR. Experimental animal models showed some efficacy with intravitreal triamcinolone acetonide or topical and systemic corticosteroids, but clinical trials in patients showed a poor response.^{85–87} A prospective, randomized controlled study of intravitreal triamcinolone acetonide injection at the time of pars plana vitrectomy with SiO tamponade in grade C PVR showed no improvement in anatomic success, visual acuity, or PVR development.⁸⁸ Triamcinolone acetonide is sometimes employed in retinal detachment repair for vitreous staining, but a large prospective multicenter study showed no difference in outcomes between patient undergoing vitrectomy with triamcinolone assisted staining and those without.⁸⁹ Additionally, the use of heparin with dexamethasone in the vitrectomy-infusion fluid during vitrectomy for PVR increased the rate of postoperative hemorrhage, but this did not impact visual outcomes.⁹⁰ A recent prospective clinical trial investigating the efficacy of slow-release 0.7mg dexamethasone intravitreal implant (Ozurdex, Allergan Inc, Irvine, CA) as an adjunct for PVR grade C treatment found no difference in the anatomic or functional success compared to vitrectomy with SiO placement without the dexamethasone implant.⁴⁶

Anti-proliferative and anti-neoplastic agents studied for PVR prevention or treatment included compounds such as 5-fluorouracil (5-FU), daunorubicin, taxol, colchicine, retinoic acid, ribozymes, vincristine, cisplatin, adriamycin, mitomycin, and dactomycin. 5-FU is an antimetabolite that inhibits synthesis and fibroblast proliferation and has been one of the most tested compounds for treatment of PVR. 5-FU showed beneficial results in animal models, but had poor results with significant side effects in humans.^{85,86} A combination therapy of steroids or 5-FU with low molecular weight heparin (LMWH), an anticoagulant that binds many growth factors, was also studied in a large, randomized, controlled trial, which did not reveal any improvement in anatomical or visual outcomes in macular-involving PVR detachments and resulted in worse visual outcomes for patients with macula sparing PVR retinal detachments.⁹¹

The Daunorubicin Study Group investigated the safety and efficacy of daunorubicin, an anthracycline antibiotic that arrests cell proliferation and cell migration, during vitrectomy in eyes with PVR. They found that daunorubicin use resulted in a small reduction in the reoperation rate in PVR patients undergoing retinal surgery. There was no difference in visual acuity and reattachment rate at one year.⁹² DNA-RNA chimeric ribozymes that target proliferating cell nuclear antigen (PCNA) showed promise in pre-clinical studies, but failed to demonstrate anatomical or visual benefits in multicenter clinical trials for PVR.^{93,94}

Anti-VEGF agents have been shown to be effective at inhibiting experimental models of PVR through inhibition of indirect PDGFR activation.⁹⁵ A prospective trial of patients with PVR grade C undergoing vitrectomy with silicone oil (SiO) placement randomized patients to receive intravitreal bevacizumab 1.25mg at the conclusion of the case, and the results showed no difference in visual acuity, redetachment rate, and PVR recurrence between the groups receiving and not receiving bevacizumab at 7 months.⁹⁶ Similar results were observed in a patients with PVR grade B or better.⁹⁷

Retinoic acid promotes growth arrest of RPE cells *in vitro*. A small (n = 35) prospective randomized clinical trial of oral retinoic acid use in patients with PVR grade C undergoing vitrectomy, demonstrated significantly lower the rates retinal re-detachment and macular pucker formation and improved vision in patients being treated with oral retinoic acid.⁹⁸ A larger prospective randomized controlled trial has been conducted and the results are forthcoming.

Methotrexate has been found to inhibit an *in vitro* model of PVR by inhibiting cell proliferation and inducing regulated cell death.⁹⁹ One retrospective study evaluating patients with severe recurrent PVR and tractional retinal detachment or severe intraocular inflammation at high risk for PVR found that these patients had a lower incidence of PVR when treated with intravitreal methotrexate infusion during vitrectomy.¹⁰⁰ Methotrexate has been shown to be safe and well tolerated in silicone-filled eyes¹⁰¹ and is currently being studied using serial injections in post-operative PVR eyes with silicone-oil.

Several additional agents have been found to be effective at preventing or treating *in vitro* and *in vivo* models of PVR. Taxol and colchicine are agents that function to stabilize and inhibit microtubule formation, which could reduce migration and proliferation of cells. These agents were found to be successful in pre-clinical models of PVR.¹⁰² Glucosamine is an inhibitor of N-linked oligosaccharide biosynthesis and processing, which suppresses RPE cell proliferation *in vitro* and interferes with the TGF- β signaling pathway in RPE cells.¹⁰³ Kinase inhibitors, such as hypericin or herbimycin, have shown positive results in preclinical PVR studies.^{104,105} Alkylphosphocholine is an inhibitor of protein kinase C shown to be effective against RPE cell attachment, migration, and proliferation *in vitro*.¹⁰⁶ AG1295, an inhibitor of PDGFR kinase, significantly attenuated the development of retinal detachment without histologic or functional damage to the retina.¹⁰⁷ N-acetylcysteine (NAC) is an antioxidant that showed efficacy in rabbits by blocking activation of the PDGFR- α and protecting rabbits from developing retinal detachment.¹⁰⁸ Epigallocatechin gallate, resveratrol, and curcumin are three polyphenolic agents that were tested *in vitro* with regards to their effect on proliferation of human RPE cells. Resveratrol was found to be the most potent.¹⁰⁹ The inhibition of Rho-kinase has also been explored because of its effect of retinal cell survival and glial reactivity. In a retina culture, Rho-kinase inhibition had neuroprotective effects by attenuating the glial cell reactivity.¹¹⁰ Palomid 529 (Paloma Pharmaceuticals, Jamaica Plain, MA) is an inhibitor of the Akt/mTOR pathways that regulates intracellular signaling involved in cell cycle control. Palomid 529 suppressed Muller cell proliferation, glial scar formation, and photoreceptor death in an experimental model of retinal detachment in rabbits.¹¹¹ HC-HA/PTX3, a soluble matrix component of amniotic membrane has been found to inhibit RPE cell proliferation and epithelial-mesenchymal transition *in vitro*.¹¹² The use of caspase inhibition has been studied extensively in experimental models, but few clinical trials have been conducted.¹¹³

Despite positive results in pre-clinical models of many agents, most of these therapies have failed to show efficacy in large prospective human clinical trials. This may be due to inadequate PVR animal models, an incomplete understanding of the disease pathophysiology, and the heterogeneous nature of PVR, which may not entirely be appreciated with current grading schemes.^{85,86}

Surgical treatment of PVR

Given the lack of pharmacologic options for PVR, the mainstay of treatment for retinal detachments with PVR is surgical intervention. The surgical goals of retinal detachment with PVR is to reattach the retina as with all retinal detachments, however, the presence of pre- and sub-retinal membranes and intraretinal fibrosis in more severe grades of PVR often require additional maneuvers to relieve traction in order to reattach the retina and prevent re-detachment.² The ideal timing of surgery for PVR is controversial. Some propose that the presence of clinical signs of activity may be an indicator to delay surgical intervention by a few weeks because the controlled trauma induced by additional surgery could stimulate additional cellular proliferation.^{4,114} Epiretinal proliferation in PVR takes an average of 6–12 weeks to develop completely. Delaying surgery would allow greater ease with membrane peel and ensure a more complete removal of the membranes.¹¹⁴ The decision to delay surgery must be balanced with the macula status and implications on visual recovery potential with further delay.

20-, 23-, 25- and 27-gauge vitrectomy have been found to be safe and effective in managing retinal detachments with PVR.^{115–121} Smaller gauge, transconjunctival vitrectomy techniques have not been found to yield superior outcomes, but may result in reduced post-operative inflammation.¹¹⁵ Scleral buckling (SB) is a surgical method that involves placement of a silicone band encircling the eye, which helps to support retinal breaks, support the vitreous base, and decrease anterior-posterior traction.^{114,122} The anatomic success rate with primary SB surgery for severe PVR retinal detachments is 34–47%.¹¹⁴ One study found that in cases at high risk for postoperative PVR, combined vitrectomy and SB was associated with higher anatomical success compared to vitrectomy alone.¹²³

Complete removal of the vitreous, including close vitreous base shaving, with scleral depression, if necessary, is recommended. Staining with triamcinolone acetonide is recommended to ensure a posterior vitreous detachment has been completed and that there is no residual posterior hyaloid and to better visualize the peripheral vitreous.

All pre-retinal membranes should be removed at the time of surgery.¹¹⁴ Vital dyes such as MembraneBlue (DORC International, Zuidland, the Netherlands) can be used to help visualize the PVR pre-retinal membranes. Indocyanine green dye can also be used to stain the internal limiting membrane (ILM) around the pre-retinal membranes to facilitate removal of the ILM and the overlying pre-retinal PVR membranes. Posterior pole ILM peeling in the absence of posterior pole pre-retinal PVR has also been advocated. Studies have found that posterior pole ILM peeling reduces the recurrence of posterior epiretinal membrane formation and one study found it reduced the risk of re-detachment.^{124–127} Further study is needed to assess the benefit of posterior pole ILM peeling in cases without posterior pole PVR.

Subretinal bands have a variable effect on the ability of the retina to reattach. If the subretinal bands are preventing retinal reattachment, they can be removed through a small retinotomy over a non-visually significant portion of the band or from under the retina if a large retinectomy is being performed. Breaking the subretinal band without removal may be sufficient for reattachment. Anterior membranes along the ciliary body or lens complex may

develop in some patients. These membranes can be removed with the depression under co-axial viewing or using endoscopic viewing.¹²⁸ Lensectomy should be considered in phakic patients with anterior pathology that is difficult to address due to the lens.

Perfluoro-n-octane (PFO) is a helpful adjunct for retinal detachment with PVR cases.¹²⁹ Prior to peeling, PFO can be used to stabilize the posterior pole. After peeling, PFO can be increased to observe if the peeling was adequate to flatten the retina. If the retina cannot be adequately mobilized or completely reattached after peeling of all the apparent membranes, it may be secondary to intraretinal fibrosis leading to contraction and foreshortening of the retina. The use of a retinotomy (relaxing incision) or retinectomy should be considered in such cases. Meticulous hemostasis at the edge of the retinectomy/retinotomy is recommended to decrease the chance of further inflammation from bleeding. Once the retinal traction has all been relieved, a fluid-air exchange followed by endolaser to the breaks and edges of the retinectomy/retinotomy is performed.¹³⁰

The last step of repair is selection of the tamponade agent, which is essential to allow time for chorioretinal adhesions to form from the laser.¹¹⁴ In the United States the options for endotamponade include air, intraocular gas, such as sulfur hexachloride (SF₆) or perfluoropropane (C₃F₈), or SiO.¹³¹ Outside of the United States, there are additional gas options and heavy silicone oil available.^{131,132}

The Silicone Study was a multicenter randomized clinical trial that compared long-acting gas with SiO for the surgical management of PVR with vitrectomy.³² The Silicone Study examined vitrectomy for PVR with long-acting gas compared to SiO for intraocular tamponade with respect to visual acuity, retinal detachment recurrence rate, and incidence of complications. It showed that SiO and C₃F₈ were equivalent with respect to management of retinal detachments with PVR and had similar rates of success with respect to anatomical and visual outcomes. Additionally, the study showed that SiO and C₃F₈ were superior to SF₆ in terms of visual outcomes.¹³³ The selection of tamponade agent must be individualized to the patient, including consideration of air travel needs and ability to return to the operating room.

Visual and anatomic outcomes in PVR

Despite repeated interventions, 10–40% of retinal detachments with PVR cases remain attached despite repeated surgery attempts.^{4,85} In one study of complicated retinal detachments mostly involving proliferative vitreoretinopathy, only 39% remained attached long term after a mean follow up period of 30 months when vitrectomy with heavy silicone oil (SiO) tamponade was used.¹³⁴ Furthermore, even with anatomic success, patients can have poor visual outcomes.⁶ Visual acuity of 5/200 or better was achieved in 40–80% of patients after repair of retinal detachments with PVR.^{4,85} The poor functional results have been attributed to possible changes in the macula, such as RPE irregularities, macular pucker, cystoid macular edema, and subretinal fibrosis.¹³⁵ These changes could also be a result of macroscopic changes secondary to formation of epiretinal, intraretinal, or subretinal membranes.¹³⁶ Anterior PVR and multiple surgeries for repair are associated with worse visual outcomes.^{2,122} In patients that demonstrate anatomic and functional success three

years after their last surgery, there is a high likelihood that results will be maintained long term.¹³³

Future directions

The use of adjunctive treatments to prevent cellular proliferation holds promise for the prevention of PVR or recurrence after surgery.⁶ Additional progress in developing grading schemes that are easy to use in clinical practice and account for the heterogeneity of PVR will be helpful in standardizing clinical PVR research. Several pre-surgical risk factors for PVR development have been identified. Further research into genetic, imaging, or biochemical biomarkers could potentially aid in the identification of the ideal patient population at risk for PVR for future clinical trials.^{45,137} While awaiting ongoing PVR clinical trial results for different agents, such as retinoic acid and methotrexate, additional pre-clinical research is continuing to identify other potential agents to ameliorate PVR formation.¹³⁸ The role of cell death in PVR is continuing to be studied and is a novel potential therapeutic target.^{139–141} Further innovations in vitreoretinal surgery devices, viewing systems, and instrumentation may also help improve surgical PVR outcomes. Ideally, in the future, pharmaceutical and surgical interventions for PVR will yield better anatomic and visual outcomes.

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Figure 1. Fundus photo of left eye with retinal detachment and proliferative vitreoretinopathy (PVR)

Fundus wide-field photograph of contracted cellular membranes associated with proliferative vitreoretinopathy leading to retinal redetachment in the setting of proliferative diabetic retinopathy. The patient was successfully reattached after membrane peel, relaxing retinectomy, and laser with silicone oil tamponade.

Figure 2. Pathophysiology of proliferative vitreoretinopathy

A retinal detachment sets off a cascade of events that can lead to proliferative vitreoretinopathy and subsequent redetachment of the retina. These events include breakdown of the blood-retinal barrier, inflammation, activation of glial and retinal pigment epithelium (RPE) cells, and retinal hypoxia. Subsequently, there is a release of cytokines, growth factors, and chemokines, which facilitate RPE cell migration, proliferation, and epithelial-mesenchymal transition. The RPE-derived fibrotic cells migrate into the vitreous and begin to lay down a membrane on the surface of the retina. The fibrotic membrane contracts and leads to recurrent detachment of the retina. Additionally, the outer retina becomes ischemic and retinal photoreceptors undergo cell death and intraretinal fibrosis occurs, leading to stiffening of the retina.

Table 1.

Proliferative vitreoretinopathy classification schemes

The three main classification schemes for proliferative vitreoretinopathy (PVR) are The Retina Society Terminology Classification (1983), the Silicone Study Classification (1989), and the updated Retina Society Classification (1991).

Retina Society Terminology Committee Classification (1983)		Silicone Study Classification (1989)		Updated Retina Society Classification (1991)	
Grade	Clinical signs	Grade	Clinical signs	Grade	Clinical signs
A (minimal)	Vitreous haze and pigment clumps	A	Vitreous haze and pigment clumps	A	Vitreous haze, pigment clumps, and pigment clusters on inferior retina
B (moderate)	Surface retinal wrinkling, rolled edges of the retina, retinal stiffness, and vessel tortuosity	B	Surface retinal wrinkling, rolled edges of the retina, retinal stiffness, and vessel tortuosity	B	Wrinkling of inner retinal surface, retinal stiffness, vessel tortuosity, rolled and irregular edge of retinal break, and decreased mobility of vitreous
C (marked) (i) C-1 (ii) C-2 (iii) C-3	Full-thickness fixed retinal folds in (i) One quadrant (ii) Two quadrants (iii) Three quadrants	P (posterior) P1: One quadrant (1–3 clock hours) P2: Two quadrants (4–6 clock hours) P3: Three quadrants (7–9 clock hours) P4: Four quadrants (10–12 clock hours) (i) Type 1 (focal) (ii) Type 2 (diffuse) (iii) Type 3 (subretinal)	Starfolds and/or diffuse contraction in posterior retina and/or subretinal membrane in posterior retina (i) Starfold (ii) Confluent irregular retinal folds in posterior retina; remainder of retina drawn posterior; optic disc that may not be visible (iii) “Napkin ring” around disc or “clothesline” elevation of retina	CP (posterior) (i) Type: (a) Focal (b) Diffuse (c) Subretinal	Full-thickness retinal folds or subretinal strands posterior to equator (1–12 clock hours of involvement) (a) Starfolds posterior to vitreous base (b) Confluent starfolds posterior to vitreous base; optic disc that may not be visible (c) Proliferation under the retina; annular strand near disc; linear strands; moth-eaten-appearing sheets
D (massive) (i) D-1 (ii) D-2 (iii) D-3	Fixed retinal folds in four quadrants that result in (i) Wide funnel shape (ii) Narrow funnel shape (iii) Closed funnel without view of the optic disc	A (anterior) A1: One quadrant (1–3 clock hours) A2: Two quadrants (4–6 clock hours) A3: Three quadrants (7–9 clock hours) A4: Four quadrants (10–12 clock hours) (i) Type 4 (circumferential) (ii) Type 5 (perpendicular) (iii) Type 6 (anterior)	Circumferential and/or perpendicular and/or anterior traction on anterior retina (i) Irregular retinal folds in the anterior retina; series of radial folds more posteriorly; peripheral retina within vitreous base stretched inward (ii) Smooth circumferential fold of retina at insertion of posterior hyaloids (iii) Circumferential fold of retina at insertion of posterior peripheral retina anteriorly; ciliary processes stretched forward; trough of peripheral retina with possible hypotony; iris retracted	CA (anterior) (i) Type: (a) Circumferential (b) Anterior	Full-thickness retinal folds or subretinal strands anterior to equator (1–12 clock hours involvement), anterior displacement, and condensed vitreous strands (a) Retina contraction inwards at the posterior edge of the vitreous base; with central displacement of the retina; peripheral retina stretched; posterior retina in radial folds (b) Anterior contraction on the retina at the vitreous base; ciliary body detachment and epipiliary membrane; iris retraction