



## Case report

## The role of vitreous cortex remnants in proliferative vitreoretinopathy formation demonstrated by histopathology: A case report

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## ARTICLE INFO

## Keywords:

Retinal detachment surgery  
 Vitreoschisis  
 Vitreous cortex remnants  
 VCR  
 Proliferative vitreoretinopathy  
 PVR

## ABSTRACT

**Purpose:** The pathogenesis of proliferative vitreoretinopathy (PVR), the most important cause of retinal detachment surgery failure, is still not fully understood. We previously hypothesized a causal link between vitreoschisis-induced vitreous cortex remnants (VCR) and PVR formation. The purpose of this case report is to demonstrate this association by showing the clinical occurrence of PVR in the presence of VCR across the retinal surface, illustrated by histopathological analysis.

**Observations:** A 69-year-old male was referred because of widespread epiretinal membrane formation after treatment of recurrent retinal detachments. During surgery with extensive membrane peeling, a large continuous membrane was peeled from the superior arcade towards the inferior temporal mid-periphery. Histopathological analysis of this membrane revealed areas with different characteristics: paucicellular laminar collagen-rich areas, suggestive for VCR, areas with increased cellularity, and more fibrotic areas with low cellularity.

The immunohistochemical analysis identified cell type variety in these areas: collagen-rich areas showed glial cells and hyalocytes, while in areas with high cellularity fibroblasts, macrophages and retinal pigment epithelial cells were found, which have previously been shown to play an important role in the development of PVR as they can transdifferentiate into myofibroblasts, which were seen in the more fibrotic areas.

**Conclusions and importance:** These findings support the theory that VCR have a role in PVR development, where VCR can act as a scaffold for fibrocellular proliferation. We suggest that the presence of VCR over the retinal surface should be qualified as a risk factor for PVR formation. Detection and adequate removal of VCR may improve the success rate of retinal detachment surgery.

## 1. Introduction

In most cases, surgery for primary rhegmatogenous retinal detachment (RRD) is successful, while additional surgery is required in about 10%, resulting in less favorable visual outcomes.<sup>1</sup> The most important cause of failing RRD repair is the development of proliferative vitreoretinopathy (PVR), a clinical syndrome associated with the formation of proliferative, contractile cellular membranes, which may result in retinal traction and subsequent development of a retinal detachment, macular pucker and macular hole.<sup>2–5</sup>

The pathophysiology of these consequential pathologies is not yet completely clarified. However, we proposed anomalous posterior vitreous detachment (PVD) with vitreoschisis as a common etiology.<sup>6</sup> During spontaneous or surgical PVD, the inner lamellae of the posterior

vitreous cortex may separate from the retina while the outermost lamellae remain attached to the retinal surface as vitreoschisis-induced vitreous cortex remnants (VCR). The presence of these VCR on the posterior pole has already been associated with idiopathic macular pathology.<sup>4</sup>

To visualize VCR during vitrectomy, extensive targeted staining with triamcinolone acetate (TA) is necessary. Given that TA is not routinely used for vitreous removal, we believe that the presence of VCR is often missed and, therefore, underestimated.<sup>6–8</sup> We found that VCR can be much more widespread across the retina and is a far more common finding than previously thought. Also, in all patients who developed a redetachment due to PVR, VCR were present over the mid-peripheral and peripheral retina and not (entirely) removed during the first surgery, in highly myopic as well as in emmetropic eyes.<sup>6</sup>

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<https://doi.org/10.1016/j.ajoc.2021.101219>

Received 13 October 2020; Received in revised form 30 June 2021; Accepted 4 October 2021

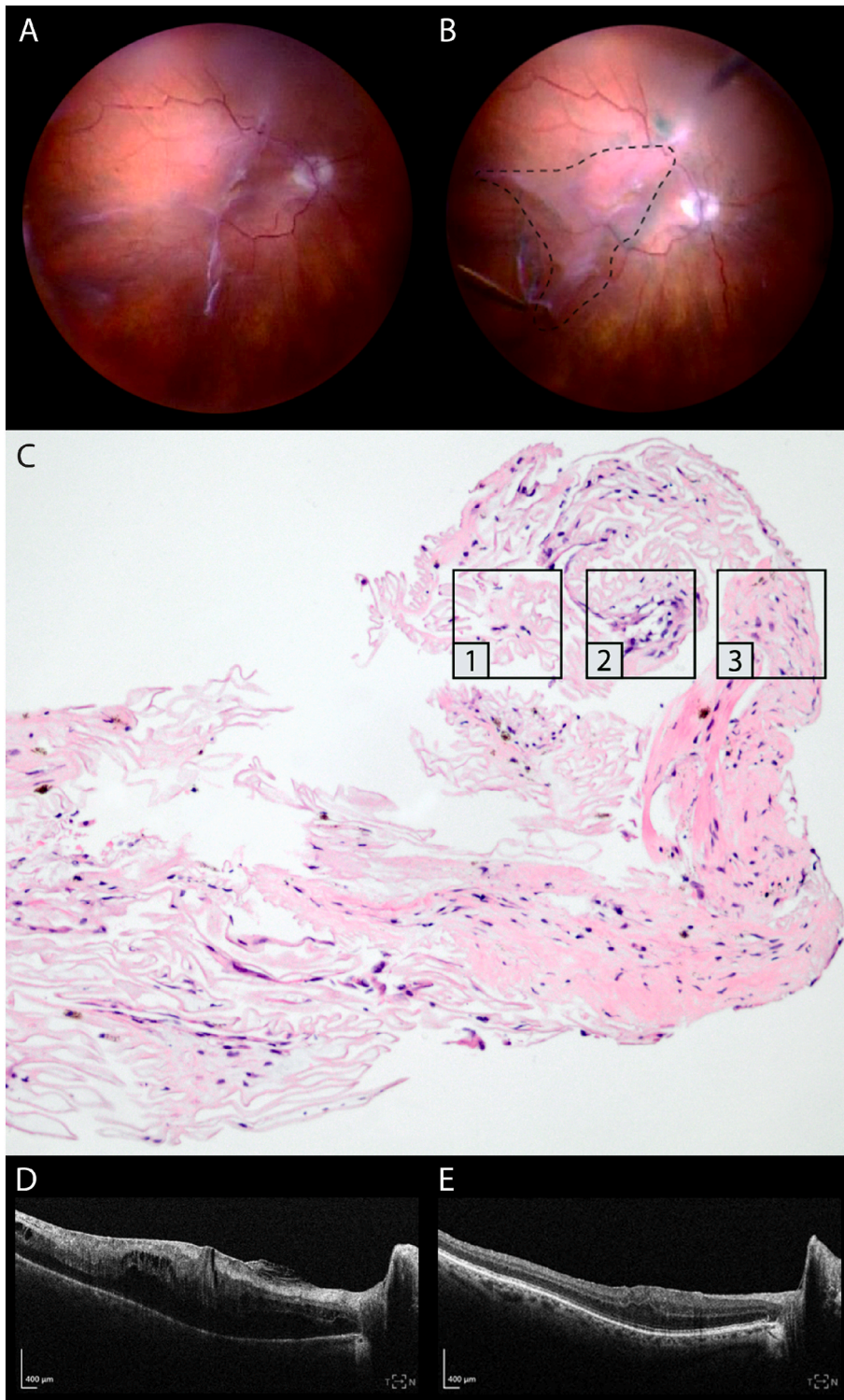
Available online 7 October 2021

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Therefore, we proposed that VCR are a causal link in the development of PVR membranes, where VCR can act as a scaffold for fibrocellular proliferation, while hyalocytes present in VCR may play a role in developing an inflammatory response and membrane formation.<sup>6</sup> This case report aims to demonstrate the relationship between the presence of VCR over the retinal surface and the formation of PVR by histopathology.

## 2. Case report

A 69-year-old male was referred to our clinic because of a rapidly progressing secondary macular pucker after multiple retinal surgeries in his right emmetropic eye (axial length 24.11 mm). A few months earlier, the patient had presented to the ophthalmology department of the referring hospital for evaluation of flashes and floaters in his right eye. Fundoscopic examination of his right eye revealed syneresis of the vitreous and a Weiss ring, suggesting PVD. In addition, a retinal horseshoe



**Fig. 1.** Fundus image at the beginning of the surgery (A) and during peeling of the epiretinal membrane, which extended from the superior arcade to the inferotemporal mid-peripheral retina (B). The dotted line indicates the area from where the membrane was removed. Microscopic image of the removed membrane stained with hematoxylin and eosin (C). Different continuous areas representing different stages of proliferative vitreoretinopathy can be distinguished: paucicellular, lamellar collagen-rich areas, suggestive for vitreoschisis-induced vitreous cortex remnants (C1); areas with increased cellular infiltration (C2); more fibrotic areas with low cellularity (C3). Pre-operative OCT image showing a significant pre-retinal membrane and an increased central macular thickness of 719  $\mu\text{m}$  (D). Post-operative OCT image at last follow-up (12 months) showed a decreased central macular thickness of 462  $\mu\text{m}$  (E). The BCVA was improved from 1.3 to 0.1 LogMAR.

tear without subretinal fluid in the superior temporal quadrant was seen, which was subsequently treated with laser retinopexy.

Despite laser photocoagulation, a macula-sparing retinal detachment developed. Therefore, a 23-gauge phacovitrectomy with sulfur hexafluoride (SF<sub>6</sub>) tamponade was performed, including peripheral shaving using triamcinolone acetonide (TA) for vitreous visualization and 360-degree laser photocoagulation at the vitreous base and around the retinal tear. No TA-assisted detection of VCR over the retinal surface was performed.

Six weeks postoperatively, the best-corrected visual acuity (BCVA) was 0.2 LogMAR and a macula-on retinal redetachment had developed in the inferior quadrants. A second vitrectomy was performed. Small retinal holes at the site of previous laser coagulates in the inferior periphery were seen intraoperatively, without signs of PVR or traction from unremoved vitreous at the vitreous base. No TA-assisted detection of VCR was performed. After additional 360-degree laser photocoagulation, the vitreous cavity was filled with SF<sub>6</sub>.

Six weeks later, a local superior retinal redetachment was found and treated with an injection of SF<sub>6</sub> gas and additional laser photocoagulation around small retinal holes at the site of previous laser coagulates in the superior periphery. Because of the complicated course of the treatment and a rapidly progressing secondary macular pucker, the patient was referred to our institute.

At presentation, 4 weeks after the last treatment, BCVA had decreased to 1.3 LogMAR. Fundoscopy revealed fibrotic tractional epiretinal membranes over the posterior pole, extending to the mid-periphery in the temporal quadrants and around the optic disc (Fig. 1A). Optical coherence tomography (OCT) showed significant puckering of the posterior pole with an increased central macular thickness of 719 μm (Fig. 1D).

### 2.1. Surgical intervention

A 23-gauge vitrectomy was performed by the first author. First, intracyanine green (2.5 mg/ml; SERB Laboratories, Paris, France) was used for staining of the internal limiting membrane (ILM) and negative staining of epiretinal membranes. A large continuous membrane was peeled from the superior arcade towards the inferior temporal mid-periphery (Fig. 1B). This membrane was sent for histopathological analysis (Fig. 1C).

After further peeling of the ILM and epiretinal membranes in the macular area and around the optic disc, remaining epiretinal membranes over the mid-periphery and periphery were peeled after staining with Membrane Blue-Dual (0.025% brilliant blue and 0.15% trypan blue; DORC International, Zuidland, the Netherlands), which was applied under air.

Finally, for the detection of vitreous at the vitreous base and VCR over the retinal surface, TA (20 mg/ml; Kenacort-A, Bristol-Myers Squibb, New York, USA) was injected towards the retinal mid-periphery, periphery and vitreous base in all four quadrants. In several areas adjacent to the already peeled retina, where TA crystals could not be removed by flushing with a backflush cannula, less-fibrotic membrane remnants could be removed.

No more vitreous was present to be removed at the vitreous base. The retina remained attached during surgery, without the development of retinal tears or hemorrhages. Limited additional laser photocoagulation was applied in two areas where membrane peeling was associated with retinal traction, and the eye was filled with octafluoropropane (C<sub>3</sub>F<sub>8</sub>) gas.

### 2.2. Outcome

The postoperative period was uneventful. Follow-up was scheduled for 1 day, 2 weeks, 6 weeks, 3 months, 6 months, 12 months, and 24 months postoperatively. At the last follow-up, BCVA was improved to 0.1 LogMAR. Although some metamorphopsia still existed, visual

function was highly improved. The retina remained attached, without any signs of PVR. The central macular thickness was decreased to 462 μm (Fig. 1E).

### 2.3. Histopathological analysis

Analysis of the epiretinal membrane revealed a continuous membrane wherein areas with different characteristics could be distinguished: paucicellular laminar collagen-rich areas, areas with increased cellularity, and more fibrotic areas with low cellularity (Fig. 1C).

Moreover, immunohistochemical analysis (data not shown) identified cell type variety in these areas: the first described areas showed glial fibrillary protein positive glial cells and hyalocytes, while in the areas with high cellularity fibroblasts, activated HLA-DR positive, CD163 positive (M2 type pro-fibrotic) macrophages and keratin positive retinal pigment epithelial (RPE) cells were found, which have previously been shown to play an essential role in the development of PVR as they can transdifferentiate into smooth muscle actin positive myofibroblasts, which were seen in the more fibrotic areas.<sup>9-15</sup>

## 3. Discussion

This clinical case supports the hypothesis that VCR can be present across the retinal mid-periphery and periphery posterior to the vitreous base, also in non-myopic eyes. A large continuous membrane extending over the central and peripheral retina was found and removed during surgery. Furthermore, the histopathological analysis supports the theory that VCR can provide a scaffold for gliosis and fibrocellular proliferation. The analysis showed paucicellular areas consisting of collagen, suggestive for VCR, that transitioned to areas of increasing cellularity and eventually fibrosis.

These different histopathological area characteristics suggest a changing composition of the membrane over time, as previously described as membrane maturation.<sup>16</sup> In concordance with other studies, this resembles different stages of a wound healing process: the initial inflammatory phase leading to a proliferative response, followed by modulation which causes contractile characteristics.<sup>10,12</sup> The variability in membrane formation across the retinal surface is likely to be determined by differences in presence and interaction of known PVR-determinants, such as hyalocytes, glial cells, RPE cells, inflammatory cells, cytokines and growth factors.<sup>13,17,18</sup>

Previous studies have already emphasized the essential role of vitreous in the development of PVR.<sup>19-21</sup> The PVR-determinants present in the vitreous body provide a PVR-stimulating environment, the lamellar structure of the vitreous cortex form a scaffold for fibrocellular proliferation, and the hyalocytes in cortical vitreous play a significant role in extracellular matrix synthesis and modulation of immune reaction and inflammation.<sup>19,20</sup> Therefore, complete removal of the vitreous body and cortex with shaving at the vitreous base has become a widely supported surgical goal to prevent postoperative PVR formation.

Our current and previous findings suggest that TA-assisted detection and removal of VCR over the retinal surface should also be part of a complete vitrectomy.<sup>6,8</sup> However, removing VCR can be challenging and time-consuming, depending on membrane composition, thickness, and adherence to the retina. More research is needed to determine which patients would benefit from VCR removal and to what extent VCR should be removed. This probably depends on the presence of other PVR risk factors.

Most known risk factors for PVR are non-modifiable. They are associated with intravitreal dispersion of RPE cells or breakdown of the blood-ocular barrier, which are prerequisites to PVR development. These factors include a longer duration and larger extent of the retinal detachment, greater size and number of retinal tears and the presence of vitreous hemorrhage or inflammation.<sup>21,22</sup> We propose a new, modifiable risk factor for the development of PVR: the presence of VCR over the retinal surface. Removing the VCR removes the scaffold for

fibrocellular proliferation, which may further reduce the risk of PVR formation and retinal redetachment.

In retrospect, a clinical clue to the presence of VCR was the development of retinal redetachments due to multiple small holes at laser treated sites. These holes might result from retinal traction by immature epiretinal membranes in the presence of damaged retina and blood-retinal barrier due to laser photocoagulation. Therefore, prudent use of laser over unremoved VCR seems advisable to reduce inflammation and subsequent retinal traction.

#### 4. Conclusion

This report including histopathological analyses supports our hypothesis that VCR play a crucial role in PVR development. Early detection and adequate removal of VCR may improve the success rate of retinal detachment surgery. However, more research is needed to improve the knowledge of VCR and their role in PVR formation and surgical failure.

#### Patient's consent

The patient orally consented to the publication of the case.

#### Funding

No funding or grant support.

#### Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

#### Declaration of competing interest

The following authors have no financial disclosures: KvO, EMB, RMV, CWAP.

No conflict of interest.

#### Acknowledgement

None.

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