Two-Year Clinical Outcomes of Pars Plana Vitrectomy as initial treatment for Refractory Retinoblastoma Vitreous Seeding and concurrent retinal detachment: A Retrospective Case Series Study

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February 22, 2024

Abstract

Abstract Purpose To evaluate the safety and efficacy of pars plana vitrectomy (PPV) for recalcitrant vitreous seeding from retinoblastoma and concurrent retinal detachment. Methods In this retrospective interventional case series, intravitreal chemotherapy-assisted PPV was performed in 6 patients with persistent retinoblastoma vitreous seeds and concurrent retinal detachment. Globe salvage, retinal reattachment, and visual preservation at last follow-up visit were calculated. Results Six eyes, initially classified as group D (n=4) or E (n=2) with sphere and (or) cloud vitreous seeds, received standard systemic with intravitreal chemotherapy and subsequently developed refractory vitreous seeds with concurrent retinal detachment. PPV produced complete elimination of vitreous seeds in all 6 eyes and no vitreous seeding recurred over a mean follow-up of 29.6 months. Globe salvage and complete retina reattachment were attained in all 6 eyes (100%). Last follow-up vision acuity was assessable in 4 eyes with 80% (3/4) better than 0.4. Three eyes (50%) received repeated systemic or focal treatment because of the recurrent retinal tumor. There was no case of extraocular tumor extension or systemic metastasis. Conclusion Administration of intravitreal chemotherapy-assisted PPV appears to be a safe and effective alternation for the initial treatment of refractory vitreous seeds from retinoblastoma. It is also a promising therapeutic strategy to repair concurrent retinal detachment and preserve the remaining visual function.

Two-Year Clinical Outcomes of Pars Plana Vitrectomy

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Word count: 3015

Abstract word count: 213

Brief running title: Vitrectomy in Retinoblastoma and Retinal detachment.

Keywords: Retinoblastoma, vitreous seeding, retinal detachment, pars plana vitrectomy

Tables: 2

Figures: 2

Abbreviations

PPV	pars plana vitrectomy
IIRC	international intraocular retinoblastoma classification
ICRB	International Classification of Retinoblastoma
IAC	intra-arterial chemotherapy
IViC	intravitreal chemotherapy
IVC	Intravenous chemotherapy
RD	retinal detachment
BCVA	best corrected visual acuity

Abstract

Purpose

To evaluate the safety and efficacy of pars plana vitrectomy (PPV) for recalcitrant vitreous seeding from retinoblastoma and concurrent retinal detachment.

Methods

In this retrospective interventional case series, intravitreal chemotherapy-assisted PPV was performed in 6 patients with persistent retinoblastoma vitreous seeds and concurrent retinal detachment. Globe salvage, retinal reattachment, and visual preservation at last follow-up visit were calculated.

Results

Six eyes, initially classified as group D (n=4) or E (n=2) with sphere and (or) cloud vitreous seeds, received standard systemic with intravitreal chemotherapy and subsequently developed refractory vitreous seeds with concurrent retinal detachment. PPV produced complete elimination of vitreous seeds in all 6 eyes and no vitreous seeding recurred over a mean follow-up of 29.6 months. Globe salvage and complete retina reattachment were attained in all 6 eyes (100%). Last follow-up vision acuity was assessable in 4 eyes with

80% (3/4) better than 0.4. Three eyes (50%) received repeated systemic or focal treatment because of the recurrent retinal tumor. There was no case of extraocular tumor extension or systemic metastasis.

Conclusion

Administration of intravitreal chemotherapy-assisted PPV appears to be a safe and effective alternation for the initial treatment of refractory vitreous seeds from retinoblastoma. It is also a promising therapeutic strategy to repair concurrent retinal detachment and preserve the remaining visual function.

. Introduction

Retinoblastoma is the most common intraocular malignant tumor in children. Even though the conservative managements witness impressive improvements in preserving life with good vision and no comorbidity[1], vitreous seeding has always remained a major concern. Spontaneous vitreous seeding at diagnosis (primary seeding) was first regarded as "very unfavorable" with poor prognosis compared to complicate the disease at tumor relapse (secondary seeding) and classified as the most severe group (Vb) by Reese[2]. Then international intraocular retinoblastoma classification (IIRC) defined diffuse massive vitreous seeding as Group D-E with a much higher risk and usually inevitable for enucleation[3]. International Classification of Retinoblastoma (ICRB) also found 56% of patients with diffuse seeds showed failure ocular outcome by chemoreduction[4]. Until the introduction of new targeted chemotherapy modalities, intra-arterial chemotherapy (IAC) and intravitreal chemotherapy (IViC), allowed much better control of intraocular seeding, however, many patients still showed persistent vitreous seeding after standard Intravenous chemotherapy (IVC) treatment combined with IviC[5-6] or IAC[7] which was regarded as "refractory vitreous seeds". Afterward, Munier and associates found the different therapeutic response of vitreous seeds to intravitreal melphalan was closely related to their distinct morphologic features, and classified vitreous seeds in three patterns: Class 1 (dust), Class 2 (spheres), and Class 3 (cloud)[8], and Class 3 seeds were the most difficult to eliminate[9]. Therefore, more effective and targeted treatment was needed for refractory vitreous seeds, especially for Class 3 seeds.

In addition, concurrent retinal detachment (RD) in retinoblastoma was another severe visual threatening factor. The incidence of RD was 67% (42/62) in a retrospective research, without any surgery repair, 16% of those patients would develop persistent RD with more advanced RB stage[10]. The incidence of rhegmatogenous retinal detachment merged from 1.5% by systemic chemotherapy concomitant cryotherapy[11] to 8% by IAC[12], which was closely related to the rapid regression of retinal tumors and atrophic retinal holes. But conservative treatments like non-drainage scleral buckling or laser barricade had little effect on RD repair as initial treatment[12]. As a result, the management of RD associated with retinoblastoma remains problematic, particularly in patients with visual potential.

In recent years, planned PPV combined with intraocular chemotherapy has been applied for the treatment of refractory vitreous seeding as an alternative to enucleation in patients with only one remaining eye, this therapeutic strategy was regarded as safe after planned systemic and focal chemotherapy, and globe salvage was attained in 85.7-100% cases[13-16]. In this case, PPV may also be beneficial for patients under lower risk with unilateral retinoblastoma and recalcitrant vitreous seeds. Meanwhile, PPV also showed successful anatomical and functional improvement in retinoblastoma patients with recurrent RD after scleral buckling[17]. However, no consensus existed on interval before considering PPV for RD repair, and the effect of PPV under different patterns of RD remained unclear. Therefore, in this study, we attempted chemotherapy-assisted PPV as initial treatment for refractory retinoblastoma vitreous seeds and concurrent retinal detachment in unilateral retinoblastoma cases.

Materials and Methods

This retrospective study was conducted between June 2018 and July 2019 in Zhongshan Ophthalmology Center, Sun Yat-sen University. Vitreous seeds persisted after at least 3 circles of standard IVC and IViC were regarded as refractory seeds, and patients diagnosed with refractory vitreous seeds with concurrent retinal detachment were enrolled. This study was performed with patients' and their families' informed written consent, and approved by the Board of Ethics at Zhongshan Ophthalmic Center, Sun Yat-sen University.

Before PPV, systemic chemotherapy with a standard CEV regimen (carboplatin, etoposide, and vincristine) and IViC (topotecan) were performed in all 6 patients to achieve the regression and calcification of subretinal tumors (Table 1). All patients were classified as group D retinoblastoma after systematic and focal chemotherapy according to the International Classification of Retinoblastoma (ICRB) criteria[4], and the fellow eyes remained unaffected.

Clinical features of concurrent retinal detachment were assessed by fundus photography and ultrasound. Three-port PPV was performed by a 27-gauge cutter with 5 μg/mL topotecan in irrigation fluid. The visible intravitreal seeds were utterly removed by vitrectomy, and additional procedures were applied when required. Subconjunctival injection of topotecan (20 μg/0.1mL) was performed regularly at the end of the surgery. Pathologic features of vitreous seeds were analyzed by immunohistochemistry, synaptophysin antibody was used to evaluate the presence of retinoblastoma cells, CD68 was used to confirm the presence of macrophages.

All patients were closely observed to evaluate the recurrence of vitreous seeds, retinal tumor, or extraocular metastasis (Table 2). For recurrent retinal tumors, additional systemic (IVC, IViC, or IAC) and focal (laser, cryotherapy) treatments were applied until all the tumors were in a state of regression by clinical examination. Silicone oil extraction was performed when emulsification occurred.

Results

During the past 3 years, 6 eyes of 6 patients received PPV for refractory vitreous seeds from retinoblastoma (Table 1). The average age at diagnosis was 4.1 years old, ranging from 24 to 98 months. Among the 6 children, 3 were female and 3 were male, all unilateral affected, including 3 right eyes, and 3 left eyes. The contralateral eyes were not affected by the last follow-up. All the eyes included in the study were classified as stage D-E at initial diagnosis, and stage D before PPV. Vitreous seeds were classified as spheres (Class 2) and(or) clouds (Class 3) at initial diagnosis and persisted as clouds before PPV. All patients had previously undergone 3.5 circles of systemic and intraocular chemotherapy on average (range 3-4). Case 3 received one additional IViC, and case 2 was treated with additional cryotherapy for the control of the retinal tumor. All subretinal lesions were atrophied and calcified before the operation of vitrectomy.

All 6 patients had concurrent retinal detachment before vitrectomy. In 4 cases (66.6%), no visualized break was found, and retinal detachment resulted from the traction of preretinal fibrosis (Figure2. C-D) and (or) exudation after additional cryotherapy (Figure 2. A-B) or rapid regression of tumor (Figure 2. E-F). Multifocal atrophic holes were found in 2 cases (33.3%) after the second and fourth circles of IVC and IViC at the edge of the regressed tumor with associated RRD (Figure 2. G-H). The mean interval between retinal detachment and surgery repair was 1.8 months (range from 0.5 to over 4 months). Table 2 depicted pathological features of seeds, type of tumor recurrence, metastasis, additional treatments, follow-up time, and the last best-corrected visual acuity. Until July 2019, the average time of follow-up after PPV was 29.6 months (ranging from 23 to 32 months). No patient showed recurrent vitreous seeding, externalization of the tumor, or systemic metastasis during the follow-up period, and the contralateral eyes were not affected.

Success with complete elimination of vitreous seeds was achieved in all 6 patients (100%) after PPV operation, one patient received no additional treatment after PPV and her best corrected visual acuity (BCVA) was 0.5 by last follow up (Figure 1). No recurrence of vitreous seeding was noticed. Complete retinal reattachments were achieved in all 6 eyes (100%) as well, 1 patient underwent a second PPV and silicone oil replacement due to proliferation. Case 2 underwent silicone oil extraction eight months after PPV and his BCVA achieved 0.6 by last follow up.

In 3 cases, the retinal tumor recurred, occurring at a median of 7.3 months (ranging from 4 to 11 months) after PPV, all 3 eyes were treated successfully with additional systemic and focal treatment, and retinal tumors were under control. The pathological results showed that most of the seeds were necrotic materials, red blood cells, or macrophages, few viable tumor cells were detected in the vitreous fluid of 4 patients (66.6%). By the last follow-up, BCVA was assessable in 4 eyes with 80% (3/4) better than 0.4.

Discussion

Refractory vitreous seeding has always been the most significant dilemma in treating retinoblastoma, especially vitreous seed clouds (Class 3). Clouds were described as a dense cumulus-like collection of punctate vitreous opacities, which were significantly more likely to occur in the equator-ora region of the fundus in older patients (median age 32 months) with unilateral disease [18]. Conservatively, IViC and IAC were generally applied for vitreous seeding. By analyzing the outcome of vitreous seeding in 28 eyes treated with intravitreal chemotherapy, Jesse et al. found that Class 3 seeds required significantly more injections for eradication than Class 1 and Class 2 (6 vs. 3 vs. 4), which resulted in severer chemotherapy-related toxicities and ocular complications (80% vs. 50% vs. 27%), as well as a higher risk for enucleation (40% vs. 33% vs. 25%) [19]. Thus, the prognosis of patients with clouds is often poor. Jasmine and associates found that rather than IViC only, IAC combined with intraocular chemotherapy could reduce the risk and recurrence rate of vitreous, however, the decrease of electroretinography response indicated that advance ophthalmic chemotherapy was toxic to the retina, and the ocular complications (such as retinal detachment) were not described by the authors [20]. By analyzing histopathologic features of 14 vitreous seeds, cloud seeds were found mostly composed of necrotic substances, mixed with few macrophages and rarely viable cells [21], which were consistent with the pathological results in our study and it also explained their poor therapeutic response to regular chemotherapy. The administration of combined intravitreal chemotherapy (melphalan and topotecan) produced control of persistent or recurrent vitreous seeds in 9 patients (3 for Group E and 6 for Group D), all received 6 circles of standard chemotherapy and 0-8 injections of melphalan for IVC, but the visual outcomes were not determined by the author [6]. Therefore, the major request for recalcitrant retinoblastoma vitreous seeding was a more efficient therapy with minimal complications and better visual outcomes.

With the improvement of early diagnosis and surgery technology, vitrectomy has been cautiously applied for persistent vitreous seeding of retinoblastoma in recent years. Initially, patients with retinoblastoma received inadvertent vitrectomy under misdiagnosis in the combination of delayed initiation chemotherapy, consequently, their prognosis was poor, and 57% (8/14) patients died [22]. Therefore, PPV was regarded to have a high risk of extraocular metastasis for a very long time. Lately, several studies have performed planned PPV with 5ug/ml melphalan or topotecan in irrigation fluid for the only one remaining eye in children with refractory binocular retinoblastoma, as an alternative therapy for enucleation [13-14], the rate of salvaged eyes was 85.7% (18/21) to 100% (11/11), and no extraocular or systemic metastasis was reported.

While in our study, intravitreal chemotherapy-assisted PPV was applied for persistent vitreous seeds and concurrent retinal detachment in unilateral retinoblastoma. Before PPV, all patients received 3-4 circles of IVC combined with IViC to achieve the atrophy of retinal tumors, which also reduced the risk of metastasis during the following intraocular surgery. Compared to melphalan, topotecan showed a longer intra-ocular half-life [23] and was more effective in controlling refractory or recurrent vitreous seeds, especially for Asians [5-6], with lower toxicity and lower cost. Therefore, topotecan was applied in this study for IViC and PPV assistance. The cloudily vitreous seeds were thoroughly removed by vitrectomy with 5ug/ml topotecan in irrigation fluid. After PPV, no patients showed extraocular extension or recurrence of vitreous seeds. The requirement of further intraocular chemotherapy was significantly reduced, and no chemotherapy-related toxic complication (such as retinal hemorrhage or optic nerve atrophy) occurred, which played an essential role in preserving the remaining visual function.

In addition to eradicating vitreous seeds, PPV surgery also contributed to repair retinal detachment associated with retinoblastoma. Previous studies found that 67% (42/62) patients developed RD during the treatment of RB, and 16% (7/42) of those patients developed persistent RD with complex RD components [10]. Primary exudative RD tend to occur with the growth of exophytic RB and usually resolve spontaneously with the shrink of the tumor, while secondary exudative RD was more related to the excessive initial inflammation and rapid shrinkage of the tumor right after the first circle of IVC or IAC [24], which could develop mixed tractional exudative RD and usually did not resolve despite the regression of the tumor [25]. Tractional RD occurred at 6.8% as thought to be due to vitreoretinal complications in patients undergoing retinoblastoma therapy, which were induced by preretinal fibrosis, vitreous traction bands, or other proliferations [11]. Rhegmatogenous RD also accounted for 6% of patients after IAC treatments, 90% (9/10) of

those retinal holes were atrophic related to rapid tumor regression, and 10% (1/10) tore hole from posterior vitreous detachment [12]. Without the violation of the state of metastatic grace, most researchers preferred minimal invasion for RD repairs, such as buckling without subretinal fluid release, laser photocoagulation, or simple observation, but those conservative treatments tend to lead to permanent retinal detachment, in contrast, patients who received PPV with silicone oil tamponade as preferred treatment was more likely to obtain complete or partial retinal reattachment [12] with better visual outcome [17].

In our study, 66.6% (4/6) cases were tractional and (or) exudative RD without a visualized break, and 33.3% (2/6) cases were RRD due to atrophic retinal holes. Primary ERD occurred in 1 case at initial diagnosis and developed mixed TRD by preretinal fibrosis after 3 circles of IVC and IViC. Secondary ERD was found in 2 cases, which happened right after initial systemic and focal chemotherapy or additional cryotherapy. The fovea was detached in 50% (3/6) cases, and 2 patients with severe retinal detachment (over 3 quadrants) received silicone oil tamponade. By the last follow-up, 100% (6/6) eyes showed complete retinal reattachment, and one patient underwent a second PPV and silicone oil replacement due to proliferation. During the follow-up, all 6 eyes were preserved, and BCVA was better than 0.4 in 3 of the 4 assessable eyes (75%).

Although planned PPV was safe and efficient in eliminating refractory vitreous seeding and repairing RD, it could not prevent the recurrence of the retinal tumor. The incidence of new tumor development ranged from 6-45% [26], mostly presented by 3 year follow-up [27]. In our study, 3 cases showed new retinal tumor recurrence at a medium interval of 7.3 (range from 4 to 11) months postoperative, all of which were under control after additional treatment. Several studies reported that risk factors associated with tumor recurrence include initial size, younger age, subretinal seeds, and group E classification at presentation [27-28]. In our study, patients with tumor recurrence were older at initial diagnosis (70.6 vs. 28.6 months) with severer subretinal seeds (3.3 vs. 0.6 quadrants) and higher incidence of RRD (66.6% vs. 0%) before PPV. ICRB group at presentation was 66.6% (2/3) in D group and 33.3% (1/3) in E group, all with sphere and (or) cloud vitreous seeds. Therefore, we suggested RB patients with severe subretinal seeds, visualized retinal holes, greater ICRB group and older age should close monitoring of tumor recurrence during follow-up.

Unlike previous studies, we do not recommend removing subretinal calcified tissues during vitrectomy, because the calcified materials were solid hard and difficult to cut/remove with the cutter, which increased surgery duration, brought unnecessary damage to the retina, and also made no contribution to prognosis. In the study of yu et al.[14], one patient with cloud seeds received subretinal calcified tissue removal during PPV. Even though the boundary of resection was treated with laser coagulation, focal retinal tumor recurrence occurred at the edge of the previous endoresection two months after PPV under silicone oil tamponade. The tumor regressed after five times repeated IViC and retinal laser photocoagulation. Similarly, in our study, subretinal calcified seeds were removed in case 5, and the focal recurrence of the retinal tumor was noticed at the boundary of endoresection 11 months after PPV under silicone oil tamponade. The tumor regressed after two times of IViC and three times of IAC, and no recurrence was observed during follow-up. Likewise, case 6 showed focal retinal tumor recurrence on the edge of reticular retinal degeneration lesion. One could speculate that such preferred location of retinal tumor recurrence may be due to more exposure of retinoblastoma progenitor cells at thinner retinal degeneration lesions with atrophic holes, which are more likely to be activated and transformed into tumor cells.

However, there are some limitations in our study. As refractory vitreous seeding and concurrent RD is relatively rare, this small and retrospective case series only consisted of 6 patients. Additionally, postoperative follow-up in this study was still short, ranging from 23 to 32 months (29.6 months on average). Given the high risk of recurrence of retinoblastoma, long-term follow-up is required to evaluate the long-term effects.

In this study, intravitreal chemotherapy-assisted PPV was applied for recalcitrant vitreous seeds and concurrent retinal detachment in unilateral retinoblastoma. The use of preoperative and intraoperative chemotherapy ensured the safety of the PPV surgery. The direct elimination of vitreous seeds by PPV reduced the toxic complications of multiple intraocular chemotherapies and contributed to the repair of the detached retina, which further preserved the remaining visual function. Our study suggests that PPV might be considered as

an alternative initial therapy for refractory vitreous seeding of retinoblastoma as well as the associated RD.

Acknowledgment

This work was supporteded by the National Natural Science Foundation of China (grant nos. 82070972) and the Natural Science Foundation of Guangdong Province (grant nos. 2019A1515011347).

Statement of Ethics

This study was approved by the Board of Ethics at Zhongshan Ophthalmic Center, Sun Yat-sen University, and written Informed consent was obtained from the parents of all individual participants included in the study.

Conflict of Interest Statement

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from Jizhu Li or the corresponding authors.

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Figure Legends

Table 1. Characteristics of patients before PPV

Table 2. Pathological results and treatment outcomes of patients

Figure. 1. Refractory vitreous seeds and concurrent retinal detachment were successfully cured by initial treatment of PPV.

A-B: Vitreous seeds cloud persist after the third circle of IViC and IVC, associated with inferior retinal detachment (white arrow) in case 1.

C-D. Retina reattached after PPV, and no recurrence of the tumor was noticed after 27 months. The temporal subretinal tumor stayed calcified by the last follow-up.

Figure. 2. Refractory vitreous seeds and concurrent retinal detachment were successfully cured by initial treatment of PPV

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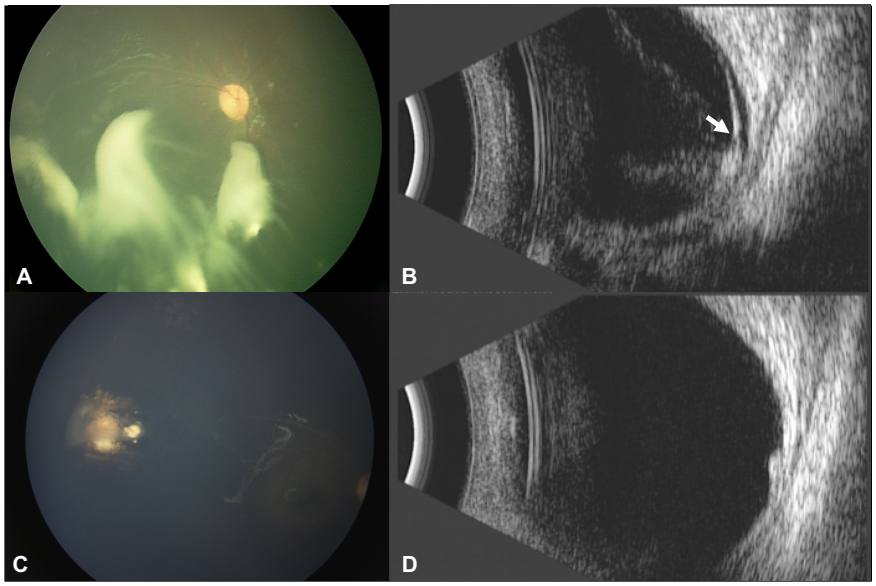

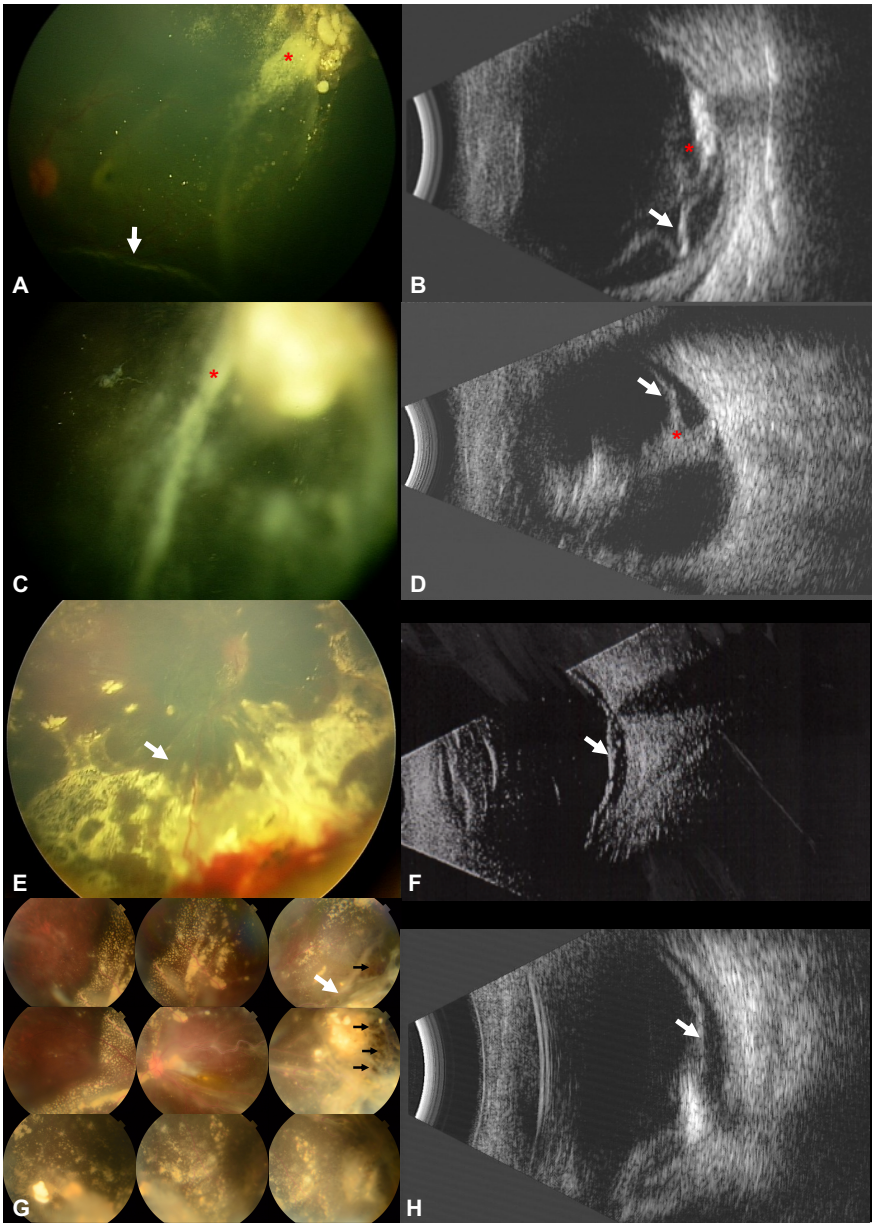

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