



Multiple serous retinal detachments after Anti-VEGF Intravitreal Injection for pachychoroid related choroidal neovascularization

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ABSTRACT

Purpose: To describe a case of serous retinal detachment (SRD) resembling Vogt Koyanagi-Harada (VKH) disease following anti-vascular endothelial growth factor (anti-VEGF) intravitreal injection (IVI) for pachychoroid related choroidal neovascularization (CNV).

Observation: A 23-year-old female complained of vision loss in her right eye (OD) one day after receiving an anti-VEGF IVI for CNV. Her best-corrected visual acuity (BCVA) in OD dropped from 20/40 to 20/200, and intraocular pressure (IOP) measured 9 mmHg. The IVI resulted in development of hypotony maculopathy, manifesting as evident chorioretinal folds. Notably, there was significant increase in choroidal thickness and dilation of choroidal vessels. Multiple SRD were observed, and fundus fluorescein angiography (FFA) findings resembled those seen in VKH. Topical and systemic steroids were prescribed to prevent inflammation, resulting in an increase in IOP and improvement in choroidal thickness and SRD.

Conclusion: Pachychoroid spectrum diseases (PSD) is associated with alterations in pachyvessel permeability and RPE damage. Hypotony maculopathy following IVI for PSD can manifest as SRD, with FFA findings resemble VKH. Careful monitoring of IOP and vigilance regarding scleral wound integrity at the injection site are imperative after IVI procedures in patients with PSD.

1. Introduction

Pachychoroid spectrum disease (PSD) is characterized by attenuation of the choriocapillaris overlying dilated choroidal veins, and associated with progressive retinal pigment epithelium (RPE) dysfunction and neovascularization. Freund and colleagues defined PSD, which encompass central serous chorioretinopathy, pachychoroid pigment epitheliopathy, pachychoroid neovascularopathy (PNV), polypoid choroidal vasculopathy, focal choroidal excavation (FCE) and peripapillary pachychoroid syndrome.^{1–5} Recent research has proposed that thickening of the sclera and stasis of the vortex vein may underlie the pathogenesis of PSD.^{6–8} Ultra-widefield indocyanine green angiography (ICGA) has revealed dilated vortex vein ampulla and stasis of the vortex vein in PSD cases. The vortex vein ampulla is typically situated in the equatorial region and exhibits a distribution across four quadrants with relative symmetry. As the vortex vein progresses towards the posterior pole, it forms watersheds with distinct functions. Intervortex venous anastomosis at the watershed have compensated for the vortex vein

stasis. Kishi described that intervortex venous anastomosis is among the key factors underlying the development of PSD.⁹ Pachyvessels, characterized by hyperpermeability, are believed to correspond to these anastomotic vessels. The stasis of the vortex vein leads to choroidal capillary occlusion and delayed filling, resulting in ischemia that can trigger various manifestations of PSD, such as choroidal neovascularization (CNV).

The term bacillary layer detachment (BLD) is a recently proposed concept based on OCT imaging. Previously described as cystoid spaces and membranous structures, BLD is characterized by the separation of the photoreceptor inner segments, forming cystic clefts.¹⁰ The formation of BLD is anatomically based on the weak structure of the inner segment of photoreceptors—myoid zone. It can be observed in various conditions such as CSC, Vogt-Koyanagi-Harada (VKH) disease, and age-related macular degeneration.^{11–13} The division of the myoid zone may be attributed to three underlying mechanisms: Firstly, photoreceptors derive nutrients from choroidal capillaries, and choroidal hypoperfusion may result in separation of the bacillary layer.¹⁴ Secondly, a large

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amount of exudate flowing rapidly into the space between the external limiting membrane and ellipsoid within the damaged RPE leads to BLD formation.¹⁵ Lastly, intrabacillary layer hemorrhage may also induce the BLD.¹⁶

Hypotony maculopathy is characterized by anatomical and functional changes resulting from low intraocular pressure (IOP). It manifests with fundus abnormalities such as papilledema, vascular tortuosity, chorioretinal folds, and infrequently, serous retinal detachment (SRD).¹⁷ While hypotony maculopathy commonly arises after glaucoma filtering surgery or penetrating eye injuries, its occurrence following intravitreal injection (IVI) is rare. A case report by Fontes et al. demonstrated that hypotony maculopathy following anti-vascular endothelial growth factor (anti-VEGF) IVI therapy.¹⁸ Here, we report a case of hypotony maculopathy presenting with SRD, BLD and fundus fluorescein angiography (FFA) findings resembling Vogt Koyanagi-Harada (VKH) disease following anti-VEGF IVI for pachychoroid related CNV.

2. Case report

A 23-year-old female underwent ranibizumab IVI in her right eye (OD) for idiopathic choroidal neovascularization (ICNV) one day prior to presentation. Unexpectedly, on postoperative day (POD) 1, the patient reported a significant decrease in visual acuity in OD. Upon revisiting the clinic, her best-corrected visual acuity (BCVA) had declined from 20/40 to 20/200 in OD. The IOP of her right eye decreased from 19 to 9 mmHg. Fundus examination of the right eye revealed multiple SRD (Fig. 1A). Optical coherence tomography (OCT) showed SRD, BLD and chorioretinal folds (Fig. 2A). Furthermore, it demonstrated highly dilated choroidal vessels (Figs. 1B and 2A) and markedly increased choroidal thickness (subfoveal choroidal thickness, SFCT: 767 μ m, the maximum thickness: 1409 μ m) (Fig. 2A). FFA demonstrated multiple pinpoint hyperfluorescent dots at the level of the RPE in the early stage and pooling of fluorescein in the subretinal space in the late stage, resembling findings seen in VKH (Fig. 1E-F).

However, the patient had received three previous ranibizumab injections in OD for ICNV, none of which resulted in SRD. Each procedure

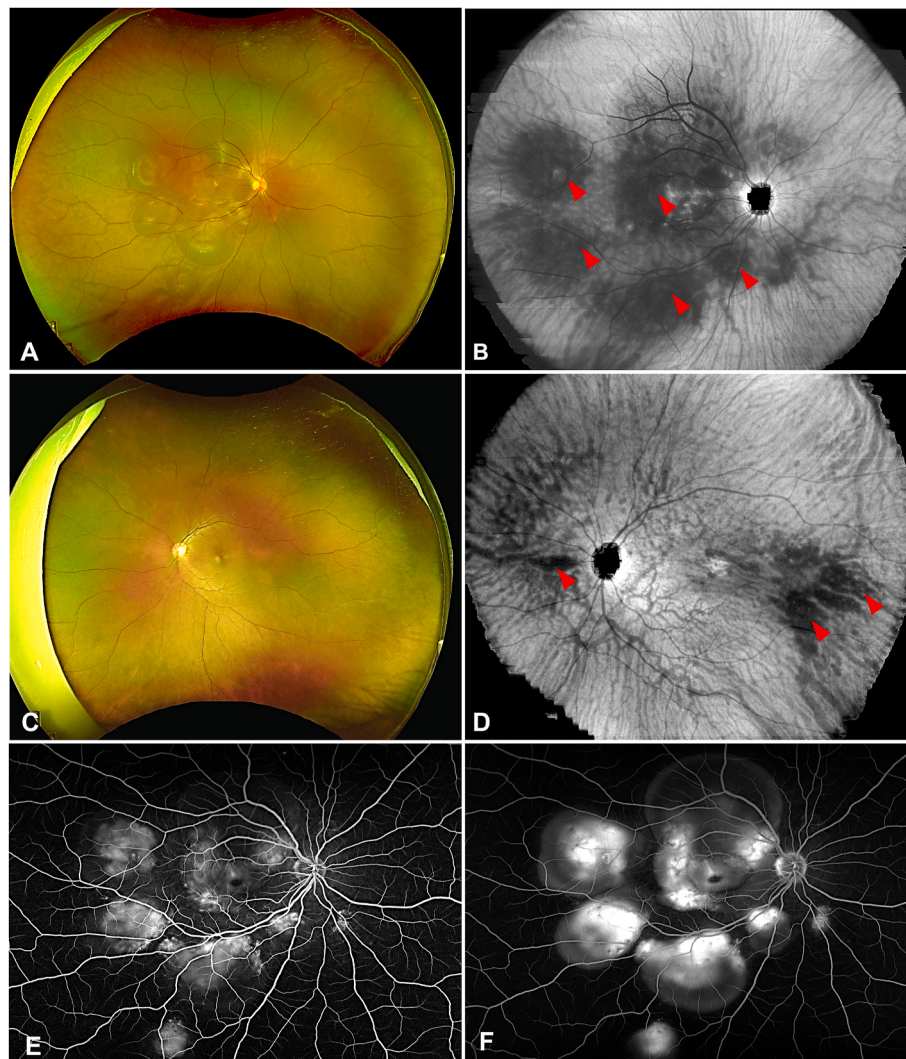


Fig. 1. Ultra-wide-field scanning laser ophthalmoscopy (UWF SLO), Ultra-wide-field optical coherence tomography (UWF OCT) and Ultra-wide-field fundus fluorescein angiography (UWF FA) images on postoperative day (POD)1. (1A) UWF SLO image in the right eye (OD) showed multiple serous retinal detachments lesions. (1C) UWF SLO image in the left eye (OS) showed no apparent abnormalities. (1B) UWF OCT enface image in choroidal layer in OD showed choroidal vessels were highly dilated (red arrows). (1D) UWF OCT enface image in choroidal layer in OS showed pachyvessels (red arrows). (1E-1F) UWF FA images in OD showed multiple pinpoint hyperfluorescent dots at the level of the retinal pigment epithelial (RPE) in the early stage and pooling of fluorescein in the subretinal space in the late stage. Fig. 2B and D were obtained using the OCT (Intalight, China). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

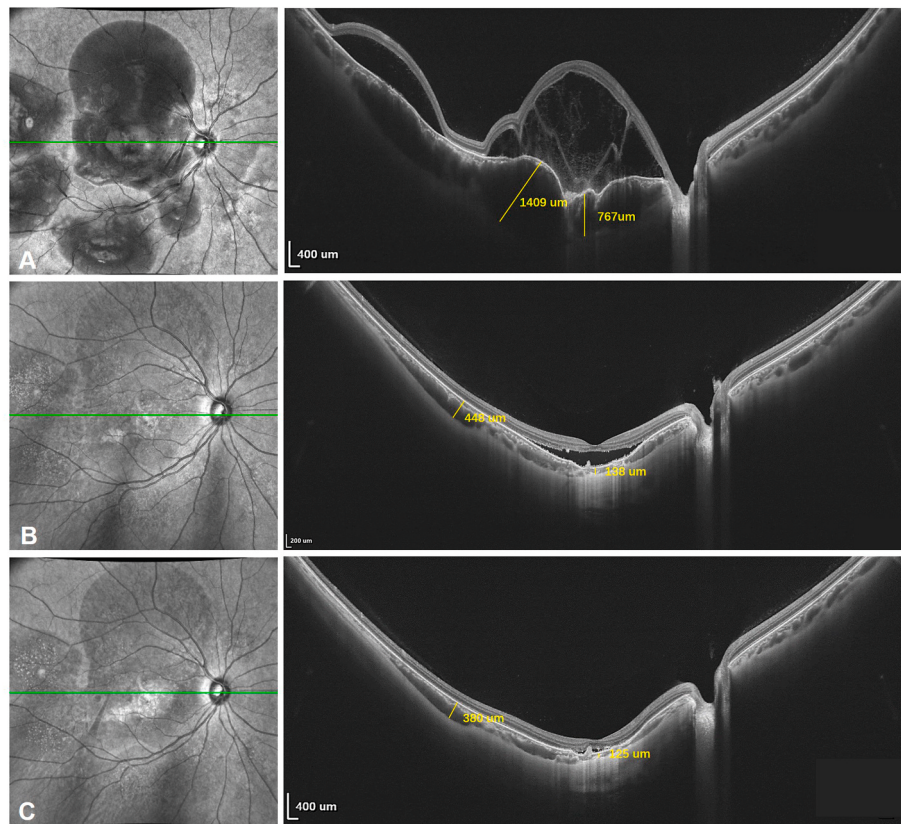


Fig. 2. Ultra-wide-field optical coherence tomography (UWF OCT) images on POD1, POD9, and POD22. (2A) UWF OCT image in OD on POD1 showed multiple serous retinal detachments, bacillary layer detachments, chorioretinal folds, and choroidal thickness was markedly thickened (subfoveal choroidal thickness, SFCT: 767µm, maximum thickness: 1409µm). Intraocular pressure (IOP) was 9 mmHg in OD. (2B) UWF OCT image in OD on POD9 showed subretinal fluid (SRF) was gradually absorbed, chorioretinal folds and choroidal thickness were improved (SFCT: 138µm, maximum thickness: 448µm). IOP was 20.9 mmHg in OD. (2C) UWF OCT image in OD on POD22 showed SRF had been nearly absorbed (SFCT: 125 µm, maximum thickness: 380 µm). IOP was 21 mmHg in OD. Fig. 2 was obtained using the OCT (Intalight, China).

was performed in the operating room. Prior to the injection, the conjunctival sac and surrounding skin were disinfected with povidone iodine. Under microscopic guidance, the injection site was precisely located using a caliper, and a 30G needle was inserted into the sclera 4mm posterior to the superior temporal limbus, with the needle directed toward the center of the globe at a depth of 8mm. After injecting 0.05ml of ranibizumab, a sterile cotton swab was used to apply pressure to the injection site, followed by the application of an eye pad. To further elucidate the etiology of SRD, we conducted a detailed review of the relevant prior examinations. Prior to this IVI, blood tests for infection and rheumatologic conditions were unremarkable. The patient denied any history of arthritis, skin changes, or ocular trauma. The BCVA was 20/40 with refraction of -3.00 diopters (D) and OCT demonstrated macular edema, subretinal fluid (SRF), and CNV in OD (Fig. 3A). Both eyes exhibited dilated choroidal vessels (pachyvessels) and localized concavities in the retina and choroid (Fig. 3A and B). Previous indocyanine green angiography (ICGA) revealed pachyvessels with hyper-permeability in OU (Fig. 3C and D). Altogether, the previous findings led to the diagnosis of PSD. It was evident that the patient had FCE in OU, and pachychoroid-related CNV in OD.

We suspected that the patient developed hypotony maculopathy following IVI. Prednisolone eye drops and oral 20mg prednisolone tablets were prescribed to reduce inflammation and improve choroidal vascular permeability. Subsequently, there was gradual absorption of the SRF, improvement in chorioretinal folds, and reduction in choroidal thickness (Fig. 2B). On POD 22, the BCVA improved to 20/40, and the IOP measured 21 mmHg in OD. OCT revealed near-complete absorption of the SRF (SFCT: 125µm, maximum thickness: 380µm) (Fig. 2C).

3. Discussion

Shimokawa et al. reported two cases of diabetic retinopathy with SRD accompanied by pachychoroid in hypotony maculopathy following trabeculectomy for neovascular glaucoma.¹⁹ Kokame et al. also reported a case of uveitis with SRD in hypotony maculopathy after glaucoma filtering surgery.²⁰ However, SRD in hypotony maculopathy is rare, and its mechanism is not well understood. Based on these cases, we hypothesize that patients who simultaneously exhibit the following two conditions may be more prone to SRD: Firstly, external factors leading to low IOP, which increases hydrostatic pressure in retinal and choroidal vessels, facilitating plasma extravasation. Secondly, internal factors such as diseases causing damage to the inner or outer blood-retina barrier. Diabetic retinopathy, uveitis, or other inflammatory conditions disrupt the inner blood-retina barrier, increases the permeability of retinal capillaries. In conditions like PSD, where there's breakdown of the outer blood-retina barrier—RPE. Increased hydrostatic pressure in retinal or choroidal vessels can lead to exudate entering the subretinal space through the weakened barrier, resulting in SRD formation.

In this case, SRD occurred rapidly, although IOP did not appear to decrease significantly. We propose three potential mechanisms contributing to this phenomenon. Firstly, it is conceivable that the IOP may have been lower immediately after the IVI, possibly due to a temporary wound leak. Subsequently, with the wound closure and secretion of the ciliary body, the IOP gradually increased by the next day when the patient revisited the clinic. Secondly, the reduction in IOP likely led to an increase in choroidal blood flow and permeability. Decreased IOP causes the ciliary body and choroid to move away from the inner surface

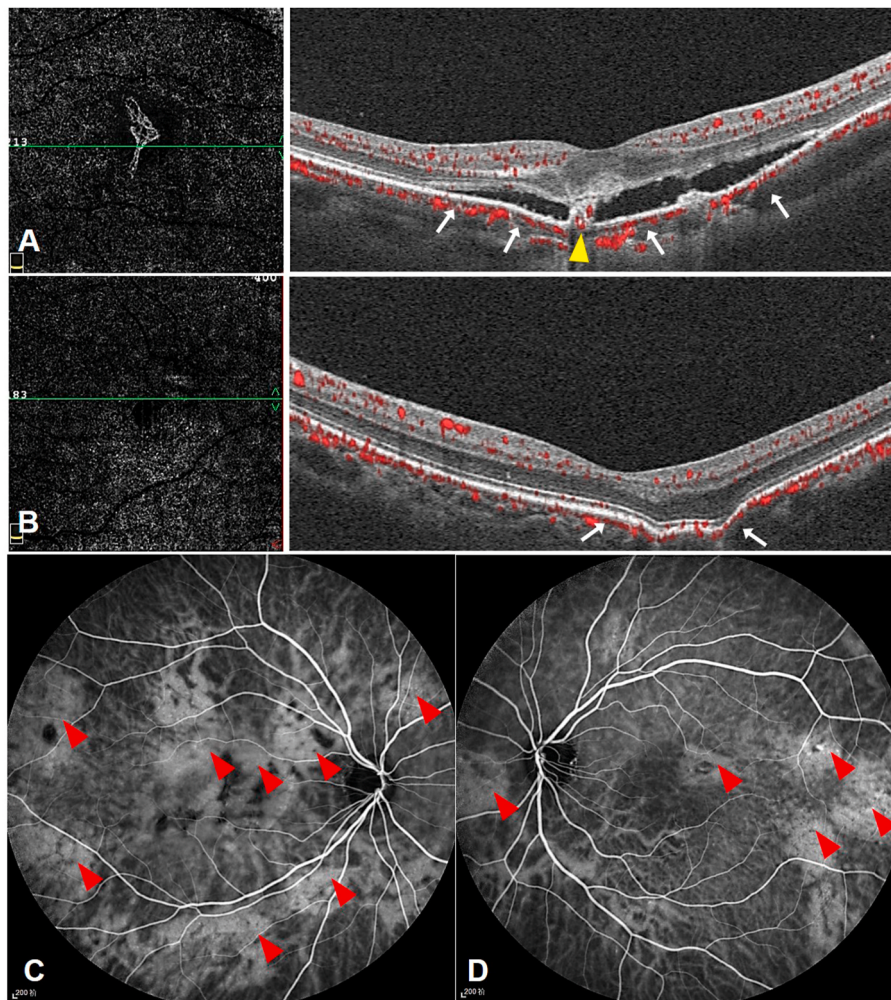


Fig. 3. Optical coherence tomography (OCT) and Indocyanine green angiography (ICGA) images before anti-vascular endothelial growth factor (anti-VEGF) intravitreal injection (IVI). (3A) OCT image before surgery in the right eye showed macular edema, subretinal fluid, choroidal neovascularization (yellow arrow), pachyvessels and focal choroidal excavation (white arrowheads), (3B) OCT image before surgery in the left eye showed focal choroidal excavation (white arrowheads), and pachyvessels. (3C-3D) Mid-phase ICGA images before surgery in the both eyes showed pachyvessels (red arrows) with hyperpermeability. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

of the sclera due to their elasticity and contraction, creating negative pressure in the suprachoroidal space. This negative pressure enhances choroidal blood flow and permeability. Previous studies have reported a negative correlation between IOP and choroidal thickness.²¹ Given the choroid is a vascular-rich tissue, changes in factors such as choroidal circulation and ocular perfusion pressure can significantly impact choroidal thickness. In this case, we noted significant thickening of the choroid and dilation of choroidal vessels under low IOP conditions. Conversely, choroidal thickness and vascular diameter decreased as IOP increased. Additionally, in the context of PSD, a pachyvessel was identified in the specimen, characterized by thin walls composed solely of endothelial cells and exhibiting high permeability.⁹ Pachyvessels are particularly susceptible to changes in IOP. Thirdly, PSD is associated with potential damage to the RPE. On the one hand, there may be delayed or occluded choroidal capillary filling due to vortex vein stasis, leading to ischemia. On the other hand, mechanical compression by pachyvessels can contribute to RPE atrophy.⁹ The sudden increase in blood flow and hydrostatic pressure in dilated and permeable vessels can result in exudate formation. This choroidal exudate may breach the weakened RPE and rapidly flows into the myoid zone, leading to the development of SRD and BLD. Therefore, these factors collectively suggest that the rapid onset of SRD in this case could be attributed to the combination of low IOP, altered choroidal blood flow and permeability,

pachyvessel characteristics, and potential RPE damage in the setting of PSD.

4. Conclusion

PSD is associated with alterations in pachyvessel permeability and RPE damage. In conditions of low IOP, pachyvessels exhibit marked dilation and increased blood flow. This scenario increases the likelihood of developing SRD, leading to diminished visual acuity. Additionally, FFA findings may resemble those seen in VKH. Consequently, it is imperative for patients with PSD to be vigilant regarding scleral wound integrity at the injection site and careful monitoring of IOP after IVI.

CRediT authorship contribution statement

Huulin Liang: Writing – review & editing, Writing – original draft, Resources. **Zhicong Xu:** Investigation. **Danling Huang:** Investigation. **Dan Cao:** Writing – review & editing, Supervision.

Patient consent

Consent has been obtained from the patient.

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Declaration of competing interest

To the best of our knowledge, the named authors have no conflict of interest, financial or otherwise.

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