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Treatment of old submacular hemorrhage by subretinal endoscopic surgery and intraoperative subretinal endoscopic findings

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ABSTRACT

Purpose: We report a case of old submacular hemorrhage (SMH) due to polypoidal choroidal vasculopathy (PCV). Subretinal endoscopic surgery (SES) was performed, which improved visual function. In addition, we show the intraoperative findings of subretinal aberrant PCV vessels as seen under endoscopic observation, which cannot be observed by microscopic surgery.

Observations: A 71-year-old Japanese man presented with an old dehemoglobinized SMH due to PCV in his left eye. At the time of presentation, three weeks had already passed after the onset of the patient's symptoms, and the best-corrected visual acuity (BCVA) was 20/200. SES was performed to remove the SMH and treat the subretinal PCV lesions. After creating retinal detachment using a 38-gauge cannula, three subretinal 25-gauge trocars were inserted from the sclera to the subretinal space. Then, SES was performed under ophthalmic endoscopic observation with continued subretinal irrigation for maintaining the retinal detachment. After removal of the SMH, subretinal polyp-shaped nodular vascular lesions (polyps) and a branching vascular network, which is located inside the retinal pigmented epithelium, were identified. The sites that presumably originated from the aberrant vessels of the PCV and the associated polyps were coagulated using endodiathermy. After the subretinal procedure, the retina was flattened with fluid/air exchange, and silicone oil (SO) was injected into the vitreous cavity. The SMH completely disappeared after surgery. Although at one-month follow-up BCVA (20/250) was slightly worse than that before surgery, there was an improvement in postoperative retinal sensitivity in the macula compared to that before surgery. At the three-month follow-up, the SO was removed. The BCVA was 20/200 one month after SO removal. No postoperative complications occurred. Additional treatment was not required, including anti-vascular endothelial growth factor therapy, for PCV progression or SMH recurrence in the left eye till the final visit two years after surgery.

Conclusion and importance: SES could effectively remove the old SMH, and the activity of PCV was suppressed by intraoperative subretinal coagulation. The retinal sensitivity of the macula improved after the SES. In addition, we observed subretinal polyps and a branching vascular network located internal to the retinal pigmented epithelium under intraoperative subretinal endoscopic observation. SES is a good surgical option for the removal of old SMH or treatment of subretinal lesions.

1. Introduction

Polypoidal choroidal vasculopathy (PCV) is thought to be a subtype of neovascular age-related macular degeneration (AMD), in which type 1 neovascularization is associated with a branching vascular network (BVN) with aneurysmal dilations, referred to as polyps.[1] Submacular hemorrhage (SMH) is an uncommon complication of neovascular AMD and has been described to occur more frequently in PCV than in typical

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AMD.[2] The occurrence of SMH can impact the visual prognosis with poor functional recovery, by an accumulation of blood between the neurosensory retina and the retinal pigment epithelium (RPE).[3] It causes a toxic effect on the surrounding tissues, resulting in loss of photoreceptors and cellular destruction in the pigment epithelium and choriocapillaris, evolving into a fibroglial scar.[4] Several surgical techniques have been proposed to displace SMH secondary to neovascular AMD.[5] Injection of subretinal air in combination with subretinal tissue plasminogen activator (tPA) for the management of subretinal hemorrhage was described recently.[6] After the original report, interventional case series in Japan, India, and USA showed favorable outcomes, further displacement of the hemorrhage, fewer postoperative complications, and earlier improvement in visual acuity than conventional SMH displacement treatments.[7–9] Sharma et al.[9] treated 24 eyes with SMH due to AMD or PCV with pals plana vitrectomy (PPV), subretinal injection of air and tPA, and partial fluid-air exchange with gas tamponade. They reported that complete displacement of the SMH from the foveal center was achieved in all 24 cases; visual acuity improved in 23 eyes and was unchanged in one eye. In Sharma's report, the average duration from onset of symptoms to surgery was 11.3 days (range, 1–59 days; median, 9 days), but it is unclear whether old SMH was included; hence, there is no consensus on the optimal management of an old SMH. In addition, Sharma et al.[9] reported that 5 of 24 eyes showed recurrent SMH after surgery and required repeat PPV, despite postoperative

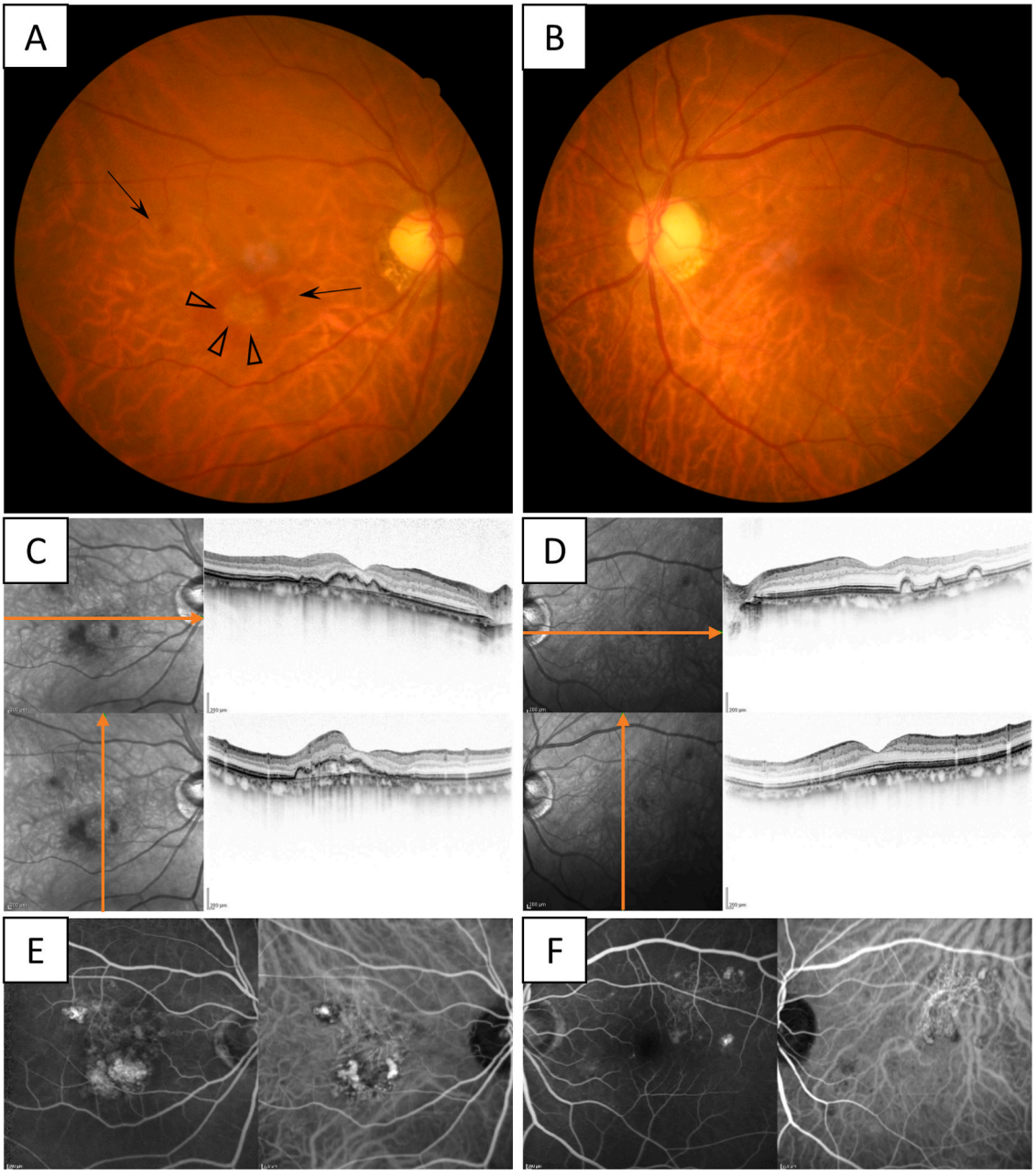

Fig. 1. Multimodal imaging of polypoidal choroidal vasculopathy of both eyes in a 71-year-old man at the first visit to our hospital. A, B: Color fundus photography (A, right; B, left). Mild macular hemorrhages around the grayish-white lesion in the macula of the right eye (A, arrows: hemorrhage, arrowheads: grayish white lesion). C, D: Optical coherence tomography B-scan images (C: right, D: left). Fibrovascular pigmented epithelium detachment, including the fovea with no intraretinal fluid and subretinal fluid in the right eye (C). Some retinal pigment epithelium elevations outside the fovea with no intraretinal fluid/subretinal fluid in the left eye (Figure D). E, F: Early-phase fluorescein angiography (left) and indocyanine green angiography (right) (E, right; F, left). Branching vascular networks and polypoidal lesions are shown as hyperfluorescent and hypercyanescent lesions in the macula in both eyes.

anti-vascular endothelial growth factor (VEGF) therapy being provided in many cases. Therefore, other treatments are desirable if continuous postoperative anti-VEGF therapy is a physical and financial burden, and postoperative treatment needs to be reduced as much as possible.

We report a case of an old SMH due to PCV that had already experienced visual deterioration for more than three weeks. This patient underwent subretinal endoscopic surgery (SES) for removal of SMH and treatment of subretinal PCV lesions. The visual function improved after surgery, and no additional treatment was required. In addition, we could directly observe the subretinal aberrant PCV vessels (polyps and BVNs) under intraoperative subretinal endoscopic observation, which cannot be observed by microscopic surgery. Here, we show the subretinal endoscopic findings and compare the findings with those of previous reports evaluated by histopathological examination and optical coherence tomography (OCT) images.

2. Case report

A 71-year-old Japanese man presented with AMD in both eyes and had a best-corrected visual acuity (BCVA) of 40/200 in the right eye and 80/200 in the left eye at the first visit (Fig. 1). Color fundoscopy showed mild macular hemorrhages around the grayish-white lesion in the macula of the right eye. OCT images showed fibrovascular pigmented epithelium detachment (PED), including the fovea, but no intraretinal fluid and subretinal fluid in the right eye and some RPE evaluations outside the fovea in the left eye. Fluorescein angiography (FA) and indocyanine green angiography (ICGA) showed hyperfluorescent/hypercyanescent BVNs and polypoidal lesions in the macula in both eyes. The patient was diagnosed with PCV in both eyes, and the right eye showed disease activity. Therefore, intravitreal injection for anti–VEGF therapy was administered in the right eye. Aflibercept was injected thrice monthly, followed by pro re nata administration of aflibercept or ranibizumab injection in the right eye. Aflibercept was injected once, followed by administration of ranibizumab thrice, and then switching back to aflibercept, which was injected thrice (18 months from the first to final injection). BCVA was 80/200 in the right eye and 120/200 in the left eye. OCT images showed no intraretinal fluid/subretinal fluid in either eye at the final administration of aflibercept injection (Fig. 2).

Two weeks after the final administration of aflibercept injection to the right eye, the patient had symptoms of central blurred vision in the left eye. Twenty-one days after the onset of the left eye symptoms, he visited our hospital. His left eye BCVA had decreased to 20/200. Fig. 3 shows multimodal imaging of his left eye. Color fundus photography revealed a whitish-yellow hematoma in the macula (Fig. 3A). The OCT B-scan image showed hyperreflective tissue over the RPE line in the center of the macula (Fig. 3B). ICGA showed hypercyanescent BVNs and polypoidal lesions in the superior temporal macular quadrant, with a hypocyanescent area due to the hematoma in the macula (Fig. 3C). Microperimetry (MP3; Nidek Co, Ltd) showed almost no retinal sensitivity in the hematoma area; the average retinal sensitivity in the 9 foveal test points was 0.4 ± 1.0 dB. The SMH had already become a dehemoglobinized hematoma (Fig. 3D). Therefore, it was expected that the old SMH would have taken a long time to absorb naturally, and retinal function impairment would have progressed. The effectiveness of anti-VEGF therapy and photodynamic therapy for old SMH is unknown. In addition, this patient had already undergone continuous anti-VEGF therapy in the right eye and was not willing to receive anti-VEGF therapy in the left eye because of the frequent hospital visits required and financial problems. Therefore, the patient wanted to undergo curative treatment by surgery. However, the effectiveness of conventional SMH displacement surgeries, including subretinal air and tPA injection for an old SMH is unknown, and the displacement of old dehemoglobinized SMH in this PCV case was expected to be difficult. In addition, SMH displacement surgeries frequently need postoperative anti-VEGF therapy even if SMH could be replaced. Therefore, SES, which can remove SMH and intervene treatment of subretinal PCV lesions, was considered a useful surgical option for this patient. The SES devised by Kaga et al.[10] is a procedure in which a three-port is inserted from the sclera to the subretinal space after creating an artificial retinal detachment (RD) using a 38-gauge cannula; subretinal surgery is performed under endoscopic observation with continuous subretinal irrigation for maintaining the RD. It was reported that severe complications such as RD or proliferative vitreoretinopathy can be avoided because of the lack of a large retinotomy. SES enables not only the removal of SMH but also the removal of fibrovascular PED and coagulation of subretinal lesions for prevention of neovascular AMD recurrence while providing observation with an ophthalmic endoscope. In this case, the patient and his family hoped to reduce postoperative intervention as much as possible; therefore, we proposed a method of removing SMH and coagulating the origin of the PCV's aberrant vessels to prevent PCV recurrence. Since SES is not a standardized treatment, we obtained approval from the ethics committee of the Japan Community Healthcare Organization Chukyo Hospital and written informed consent from the patient and his family. SES was performed after 23 days of the onset of symptoms.

2.1. Surgical procedure and subretinal endoscopic findings

After performing the phaco lensectomy and 25-gauge 3-port PPV using a Constellation Vision System (Alcon Laboratories, Inc., Fort Worth, TX), artificial RD was created as much as possible until it touched the back of the lens. It was done by injecting a balanced salt solution and filtered air from one small retinotomy into the subretinal space using a

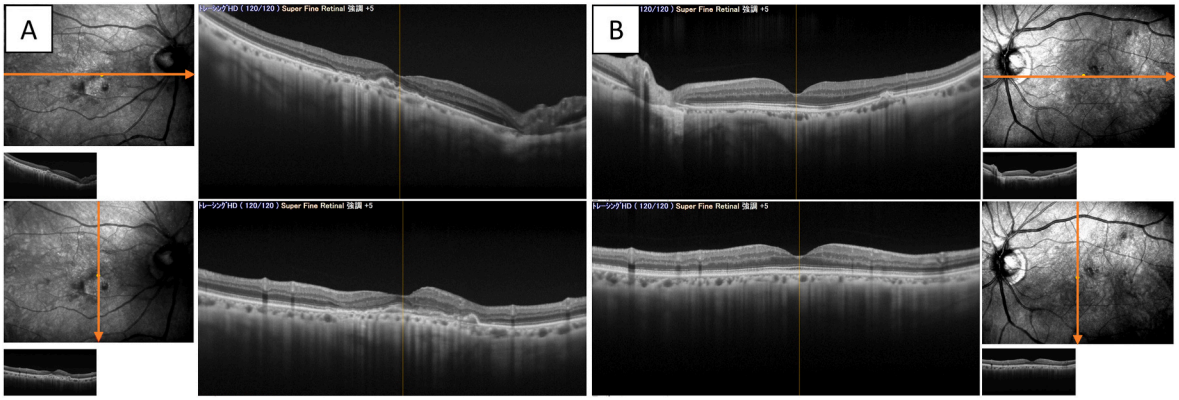

Fig. 2. Optical coherence tomography B-scan images at the final administration of injection in the right eye (A: right, B: left). Optical coherence tomography B-scan images show fibrovascular pigmented epithelium detachment (PED), including the fovea, with no intraretinal fluid and subretinal fluid in the right eye (A) and a mild PED outside the fovea with no intraretinal fluid/subretinal fluid in the left eye (B).

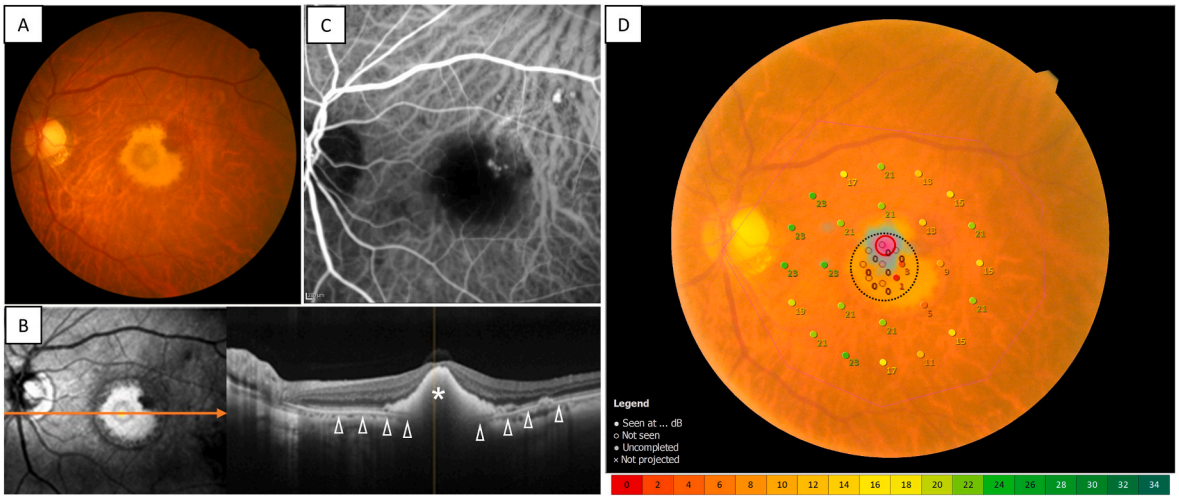

Fig. 3. Multimodal imaging of the left eye when an old submacular hemorrhage (SMH) was seen at visit to our hospital. A: Color fundus photography showing a whitish-yellow SMH in the macula. B: Optical coherence tomography B-scan image showing an SMH as a hyperreflective tissue (asterisk) over the retinal pigment epithelium line (arrowheads) in the center of the macula. C: Early-phase indocyanine green angiography shows the neovascular complex of polypoidal choroidal vasculopathy (branching vascular networks and polypoidal lesions) as hypercyanescent lesions in the superior temporal macular quadrant and hypocyanescent area due to SMH in the macula. D: Microperimetry (Nidek Co, Ltd) shows almost no retinal sensitivity in the SMH area. The retinal sensitivity in the 9 foveal test points is 0.4 ± 1.0 (average ± standard deviation) decibels (black dot circle).

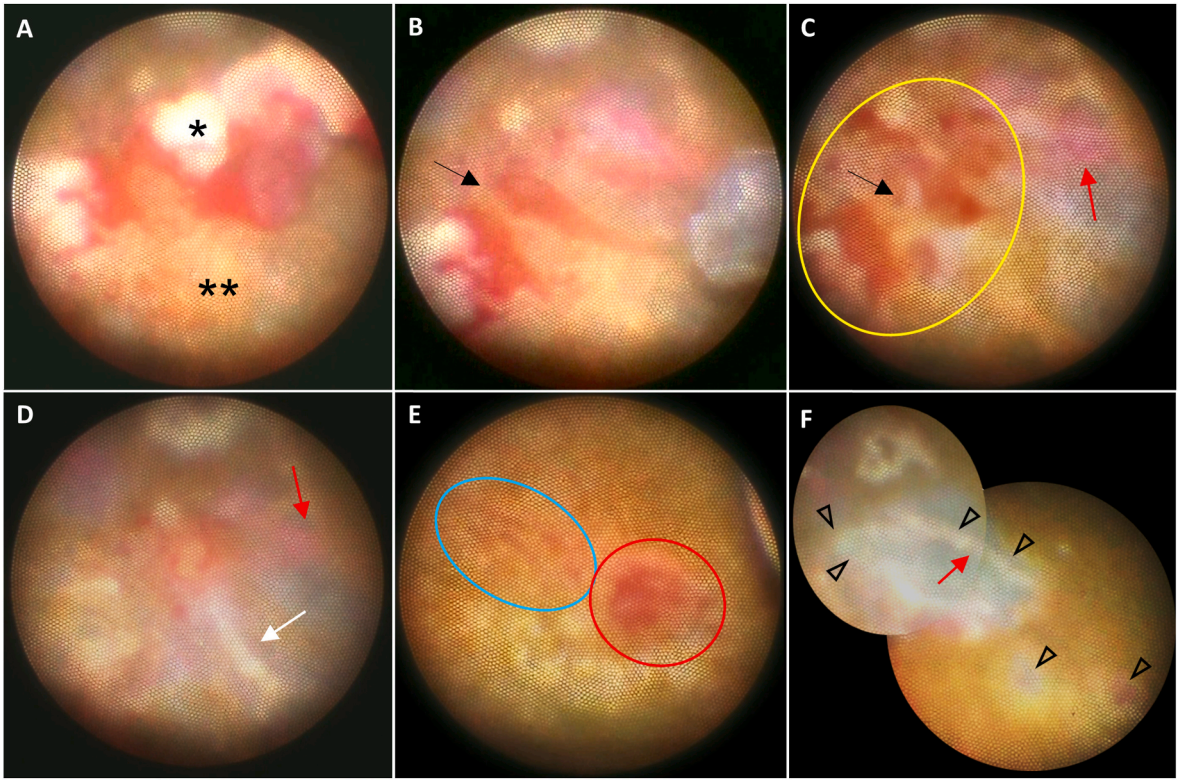

Fig. 4. Subretinal endoscopic view during subretinal endoscopic surgery. A. Image of an old whitish-yellow submacular hemorrhage (SMH) accompanied by fresh red clots below the SMH (asterisk) on the orangish retinal pigment epithelium (RPE) (double asterisks). B. After removal of the SMH, there was a bleeding point on the surface of the RPE (black arrow). C. Around the bleeding point (black arrow is the bleeding point shown in B), there are multiple irregular polyp-shaped nodular vascular lesions (yellow circle). They appear to be located inside the thin RPE, while some of them penetrate above the thin RPE. A reddish choroidal vessel is observed in the RPE defect area (red arrow). D. There was a whitish choroidal vessel in the RPE defect area (white arrow). The reddish choroidal vessel (red arrow) is the same as that indicated by the red arrow in (C). E: Image of a branching vascular network (blue circle) and a polyp located at the terminal of the branching vascular network (red circle) as observed through the RPE; they appear to be located inside the RPE. F: The presumed sites of origin of the polypoidal choroidal vasculopathy aberrant vessels, and the associated polyp lesions were coagulated by endodiathermy (arrowheads, coagulated points). The reddish choroidal vessel (red arrow in C) whitened after coagulation (red arrow).

38-gauge cannula (Extendable PolyTip; MedOne Surgical, Inc., Sarasota, FL, USA). Three subretinal 25-gauge trocars were then inserted from the sclera to the subretinal space, followed by SES under ophthalmic endoscopic observation (FiberTech, Tokyo, Japan) with continuous subretinal irrigation to maintain the RD. The SES video is shown in the supplemental digital content (see Video). First, a whitish-yellow dehemoglobinized SMH and fresh red clots below the SMH were observed on the orangish RPE layer (Fig. 4A). After removal of the SMH, there was a bleeding point on the surface of the RPE (arrow, Fig. 4B), and multiple irregularly polyp-shaped nodular vascular lesions were detected (yellow circle, Fig. 4C). They appeared to be located inside the RPE, while some of them penetrated above the thin RPE. Near these polyps, a dilated reddish choroidal vessel (red arrows, Fig. 4C and D) and a whitish choroidal vessel (white arrow, Fig. 4D) were observed in the RPE defect area. At the temporal side of the reddish choroidal vessel, a BVN and a polyp located at the BVN terminal were identified, and they appeared to be located inside the RPE (blue and red circles, Fig. 4E). The presumed sites of origin of the PCV's aberrant vessels and the associated polyp lesions were coagulated using endodiathermy (arrowheads indicate coagulated points, Fig. 4F). After this subretinal procedure, the retina was flattened with a fluid/air exchange, and silicone oil (SO) was injected into the vitreous cavity.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.ajoc.2022.101393

Fig. 5 shows a color fundus photograph and OCT images one week after surgery. The SMH had disappeared completely after surgery. Fig. 6 shows the one-month follow-up multimodal imaging after subretinal endoscopic surgery. OCT images showed no subretinal hyper-refractive tissue (Fig. 6A). In the FA/ICGA images, there was a hypofluorescent/hypocyanescent area in the superior-temporal macular quadrant (Fig. 6B). The ICGA showed no BVNs and polypoidal lesions, which were recognized as hypercyanescent lesions before the SES surgery. FA showed mild hyperfluorescent lesions that seemed to be BVNs and polypoidal lesions around the low fluorescence area. Although the BCVA (20/250) was slightly worse than it was pre-surgery, microperimetry showed improvement of retinal sensitivity in the fovea and parafovea. The average retinal sensitivity in the 9 foveal test points, which were barely visible pre-surgery (0.4 ± 1.0 dB), improved to 12 ± 7.2 dB (Fig. 6C). The patient mentioned that the black spot in the visual center disappeared and vision was better than pre-surgery. SO removal was done three months after the SES. Fig. 7 shows OCT and FA/ICGA images one month after the SO removal. The BCVA was 20/200. OCT and FA/ICGA findings were stable, and there was no SMH and PCV recurrence or progression requiring anti-VEGF therapy. No postoperative complications such as RD or proliferative vitreoretinopathy occurred, and no additional treatment was required including anti-VEGF therapy due to PCV progression or SMH recurrence in his left eye, till the final visit two years after surgery.

3. Discussion

In this patient, the old dehemoglobinized SMH was completely removed by SES, retinal sensitivity in the macula was improved after the SES, and the patient's visual symptoms also improved. However, the BCVA at the four-month follow-up after SES was 20/200, which was the same as the preoperative BCVA. The postoperative OCT B-scan images showed no disruption of the RPE in the fovea (Figs. 6A and 7A), but the postoperative OCT B-scan images one month after SMH removal showed that the line of the ellipsoid zone (EZ) and interdigitation zone (IZ) in the macula had disappeared (Fig. 6A), and the EZ/IZ line remained absent even four months after SMH removal (Fig. 7A). This indicates that the RPE structure of the fovea was preserved after SMH removal by the SES, and the retinal sensitivity of the macular was improved, but the EZ/IZ lines had disappeared, suggesting the recovery of retinal function was limited. SMH is thought to induce irreversible retinal damage within 24 hours and a total loss of photoreceptors after 7 days.[11] More than three weeks had passed since the onset of SMH in our patient, which might have caused irreversible damage to the neurosensory retina. In order to obtain good visual function after surgery, it is important to remove SMH before the neurosensory retina is irreversibly damaged, and to minimize the damage of the RPE, especially in the fovea during SES. In this patient, although tPA was not used intraoperatively, SMH can be removed more easily by using tPA in combination with SES, and surgical damage to the RPE may be reduced, indicating that better postoperative visual function may be obtained. Further studies on SES in combination with tPA are needed.

In this patient, SO was injected in the vitreous cavity because the patient had mild dementia and was expected to have difficulty maintaining a prone position postoperatively. Since SES needs the creation of artificial retinotomy and RD, intra- and post-operative complications should be considered. In a case series of 5 eyes performed SES previously reported by Kaga et al.,[10] there was no postoperative RD or other complications, but SO was injected in four of the five eyes. On the other hand, Sharma et al.[9] reported that postoperative RD in 2 eyes, macular hole in 1 eye, and vitreous hemorrhage in 3 eyes of 24 eyes had occurred after displacement of SMH with PPV, subretinal injection of air/tPA, and gas tamponade. This surgical method differs from SES, but it creates retinotomy and artificial RD, similar to as in SES. It needs to be studied in more cases whether gas or SO tamponade should be used in SES and safety and efficacy of SES.

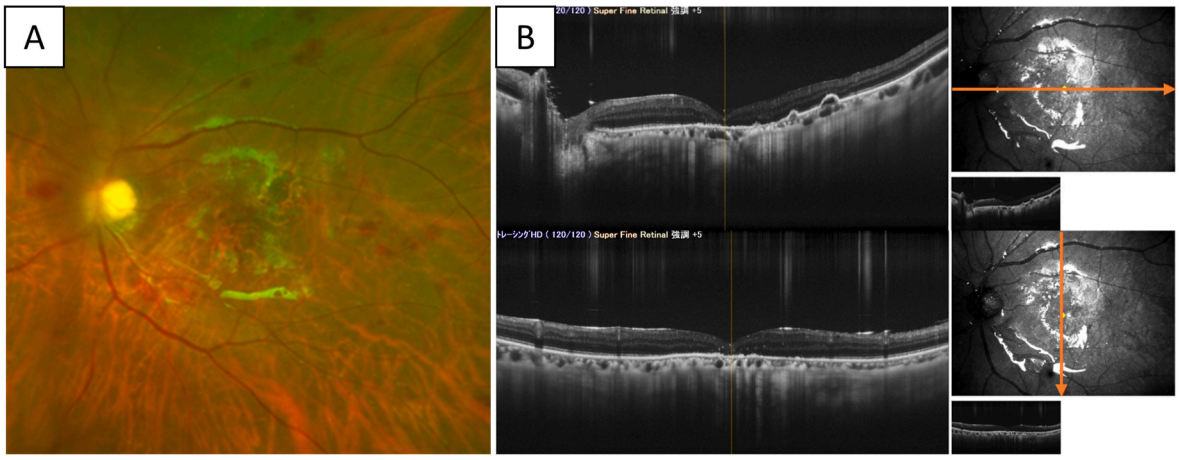

Fig. 5. At the one-week follow-up after the subretinal endoscopic surgery. A. Color fundus photography shows the complete disappearance of the submacular hemorrhage. B. Optical coherence tomography B-scan images show no subretinal hyperrefractive tissue.

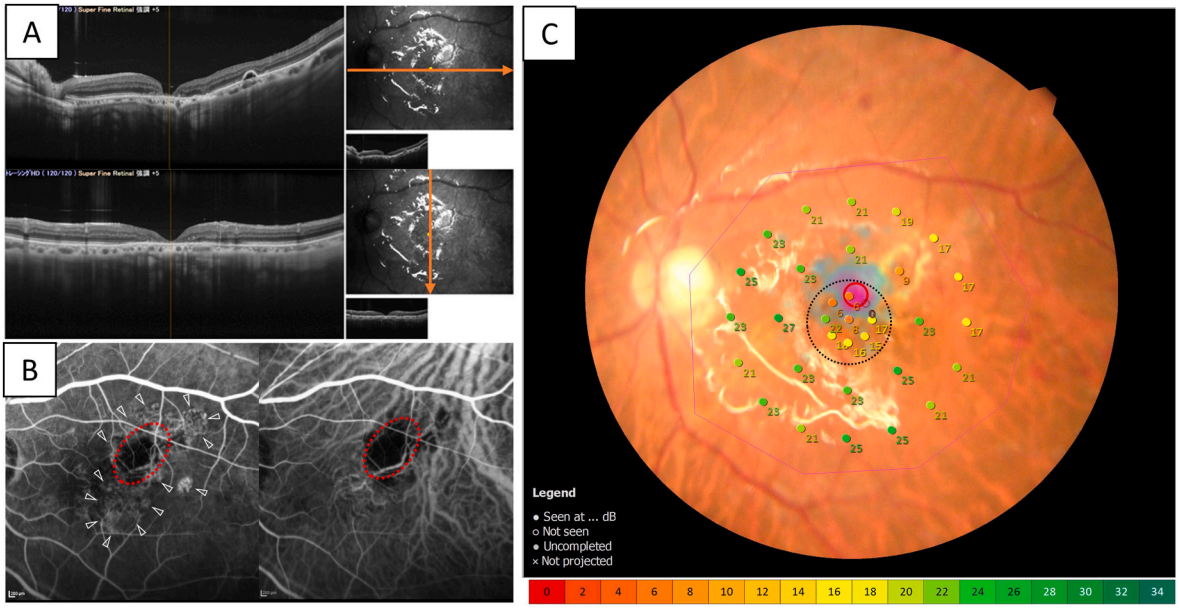

Fig. 6. Multimodal imaging after the subretinal endoscopic surgery at the one-month follow-up. A. Optical coherence tomography B-scan images show no subretinal hyperrefractive tissue. Although no disruption of the retinal pigment epithelium is noted, there is a disappearance of the line of the ellipsoid and interdigitation zone in the macula where the submacular hemorrhage was located. B. In the early phase fluorescein angiography (left) and indocyanine green angiography (right), there is a hypofluorescent/hypocyanescent area in the superior temporal macular quadrant (red circles). The fluorescein angiography shows mild hyperfluorescent lesions, which seem to be branching vascular networks and polypoidal lesions around the low fluorescent area (arrowheads, left). The indocyanine green angiography shows no branching vascular networks or polypoidal lesions (right). C. Microperimetry shows post-surgical improvement in retinal sensitivity in the fovea and parafovea, where the submacular hemorrhage was observed pre-surgically. The retinal sensitivity in the 9 foveal test points is 12 ± 7.2 (average ± standard deviation) decibels (black dot circle).

This patient did not require additional treatment, including anti-VEGF therapy, in his left eye till the final follow-up two years after surgery. It is considered that the activity of PCV can be reduced by intraoperative coagulation. However, the postoperative FA showed mild hyperfluorescent BVNs and polypoidal lesions around the low fluorescence area, which were recognized as hyperfluorescent lesions before SES surgery, despite their absence on the postoperative ICGA. This may indicate that the PCV lesions had not completely subsided. There is a possibility of recurrence of PCV lesions in the future; hence, careful follow-up is required.

An advantage of SES is that it can treat subretinal lesions under direct ophthalmic endoscopic observation, which are difficult to observe using microscopic surgery. In this patient, subretinal polyps and BVNs were directly identified by intraoperative subretinal endoscopic observation. They appeared to be located inside the RPE tissue, while some polyps penetrated above the thin PRE. When PCV was first reported, the authors described the vascular lesions as located in the inner choroid below Bruch's membrane (BrM) based on clinical observations and angiographic interpretations.[12] Subsequently, several histopathological studies described conflicting locations for PCV's aberrant vessels (intra-BrM or choroid).[13–15] In studies using spectral-domain OCT, the abnormal vascularization causing exudation in eyes with PCV (polyps and BVN) was consistently identified between an elevated RPE and the thin hyperreflective line representing the outer portion of BrM.[16–18] On the other hand, some reports found that the BVN was located in the inner choroid using swept-source OCT or OCT angiography.[19,20] The endoscopic findings in this patient may support the concept that the aberrant vessels of PCV such as the BVNs and polyps are located between the RPE and BrM.

The resolution of an endoscopic image is relatively poor as compared to the microscopic image. Recently, a proximity endoscope which can observe the fine structures has been developed,[21] and further advancement of the endoscopic image quality may reveal the subretinal lesions in greater detail. In addition, we recognize that the observations of our report are limited and not necessarily representative of the entire PCV population. However, this report is the first to demonstrate, in vivo, a nearly clinicopathological correlation in a Japanese patient with a hemorrhagic subtype of PCV.

4. Conclusions

We report the case of a patient with an old dehemoglobinized SMH due to PCV who underwent SES. The SMH was removed successfully, the retinal sensitivity in the macula was improved, and the patient's visual symptoms improved. The activity of the PCV lesion could be suppressed by intraoperative subretinal coagulation of the PCV's aberrant vessels. In addition, we observed subretinal aberrant PCV vessels (polyps and BVNs) located inside the RPE under intraoperative subretinal endoscopic observation. SES could be a surgical option for the removal of old SMH or treatment of subretinal lesions.

Patient consent

We hereby acknowledge that the patient provided written informed consent for reporting the examination and imaging findings as deemed necessary for diagnosis, education, research, and quality improvement.

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Authorship

Sho Yokoyama: Conceptualization, Investigation, Writing - Original Draft, Visualization. Takashi Kojima: Writing - Review & Editing. Tatsushi Kaga: Conceptualization, Resources, Writing - Review & Editing. Jorge Orellana-Rios: Writing - Review & Editing. R. Theodore Smith: Writing - Review & Editing. Kazuo Ichikawa: Supervision.

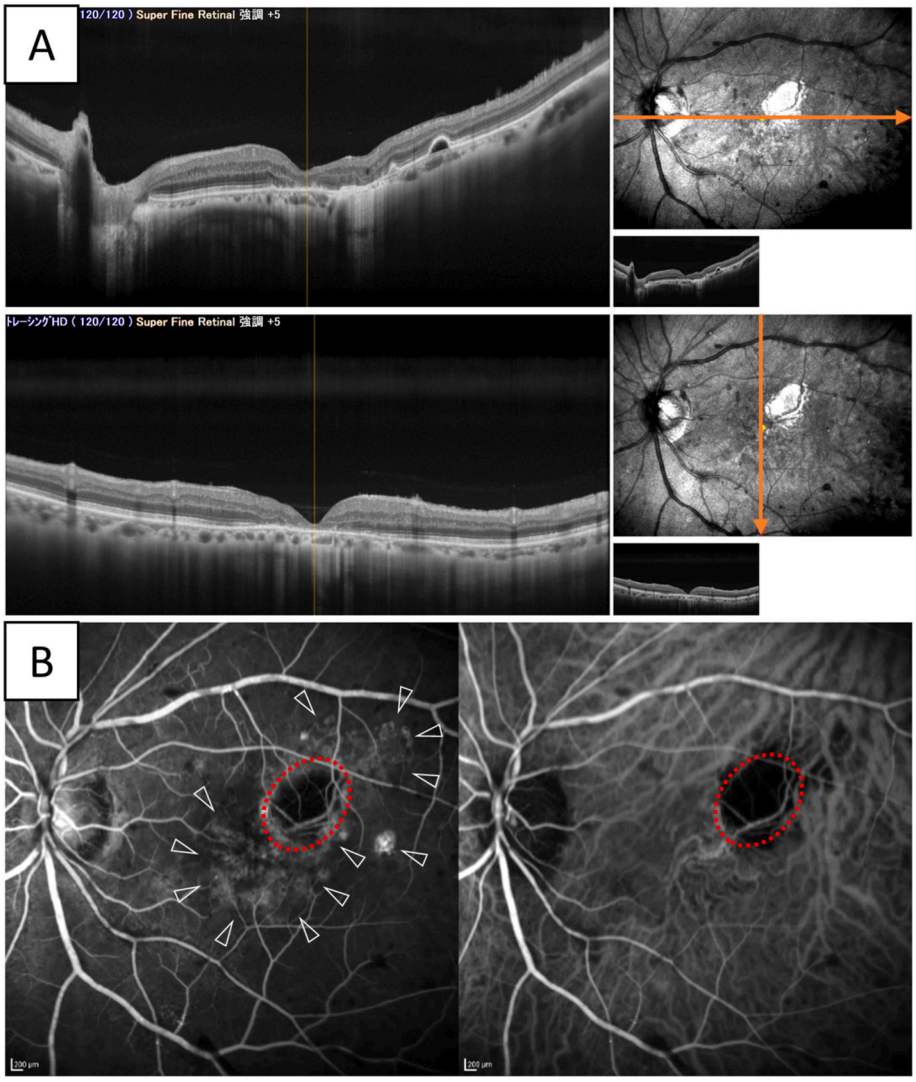

Fig. 7. At one-month follow-up after removal of silicone oil. A: Optical coherence tomography B-scan images showing no subretinal hyperrefractive tissue. As shown in Fig. 6, the line of the ellipsoid and interdigitation zone in the macula disappeared, though no disruption of the retinal pigment epithelium was noted. B: In the early phase fluorescein angiography (left) and indocyanine green angiography (right), there is a hypofluorescent/hypocyanescent area in the superior temporal macular quadrant (red circles). The fluorescein angiography showed mild hyperfluorescent lesions, which seemed to be branching vascular networks and polypoidal lesions around the low fluorescent area (arrowheads, left). The indocyanine green angiography showed no branching vascular networks or polypoidal lesions (right).

Declaration of competing interest

The following authors have no financial disclosures: Sho Yokoyama, MD. Takashi Kojima, MD, PhD, Tatsushi Kaga, MD, PhD, Jorge Orellana-Rios, MD, R. Theodore Smith, MD, Kazuo Ichikawa, MD, PhD.

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