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Case Report

Removal of Subfoveal Massive Hard Exudates through an Intentional Macular Hole in Patients with Diabetic Maculopathy: A Report of Three Cases

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Keywords

Diabetic macular edema · Diabetic maculopathy · Diabetic retinopathy · Hard exudate · Macular hole · Vitrectomy

Abstract

Recently, good postoperative visual acuity has been reported using surgical removal of hard exudates (HEs) through an intentional macular hole (iMH). We report 3 cases of subfoveal HE secondary to diabetic maculopathy (DM) treated with HE removal via an iMH. Pars plana vitrectomy (PPV) was performed in three eyes of 3 patients with subfoveal HE secondary to DM. In all eyes, after PPV, internal limiting membrane (ILM) peeling of the lower half was performed within the range of papilla diameter 2 centered on the fovea, leaving the upper half for subsequent inverted ILM flap technique. Then, by grabbing the inner layer of the fovea using ILM forceps, an iMH was created. The HE was then flushed from the iMH with a balanced salt solution as much as possible. Finally, the inverted ILM flap technique was performed using the upper half of the ILM that was left during the previous maneuver. At the end of the surgery, the eyes were flushed with 50 mL of 20% sulfur hexafluoride (SF6) after the fluid-air exchange of the vitreous cavity. After surgery, HE was adequately removed, iMH was completely closed, and visual acuity improved in all eyes. This surgical procedure did not cause a central scotoma but rather improved the central sensitivity of the visual field in all eyes. No serious surgery-related complications occurred. In conclusion, HE removal via an iMH hole can be one of the treatment options for patients with subfoveal HE secondary to DM.

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Introduction

Diabetic maculopathy (DM), manifesting as diabetic macular edema, is an important cause of visual impairment related to diabetic retinopathy (DR). The main pathophysiological factor is thought to be the disruption of blood-retinal barrier and the formation of microaneurysm (MA), which leads to leakage of plasma into the retina, resulting in diabetic macular edema and hard exudates (HE). HEs are composed of lipids and proteinaceous substances, such as fibrinogen and albumin, and usually accumulate primarily in the outer plexiform layer. When it becomes chronic, it deposits in the subfoveal region. HE deposition can cause marked deterioration of visual acuity [1, 2] due to the photoreceptor degeneration, neuronal degeneration in the outer plexiform layer [1], and blockage of the interaction between the neurosensory retina and the retinal pigment epithelium [3]. Generally, HE secondary to DM can be treated with retinal photocoagulation [4], sub-Tenon's or intravitreal injections of triamcinolone acetonide [5], intravitreal anti-vascular endothelial growth factors (VEGF) administration [6], pals plana vitrectomy (PPV) [7], or a combination of these. However, irreversible retinal damage and decreased visual acuity could develop if HE accumulated into the subretinal space for extended periods [1–3]. For such refractory HEs, surgical removal of subfoveal HE was reported to be effective [8, 9]. Originally, the surgical removal of HE was performed through an intentional retinal tear on the temporal side of the fovea [8]; however, good postoperative visual acuity has been recently reported using surgical HE removal through an intentional macular hole (iMH) [9]. Here, we report three cases of HE secondary to DM treated with surgical HE removal through an iMH.

Case Report/Case Presentation

Surgical Procedures

All surgical procedures were performed by a single experienced surgeon (HI) in the same operative room. Standard 27-gauge PPV using the Constellation Vision System (Alcon Laboratories, Inc., Fort Worth, TX, USA) with a wide-angle non-contact viewing system (Resight®; Carl Zeiss Meditec AG, Jena, Germany) was performed under sub-Tenon anesthesia with approximately 4 mL of 2% lidocaine in all cases. Three cannulas were created with conjunctival displacement and oblique-angled sclerotomies in the inferotemporal, superotemporal, and superonasal quadrants, 3.0–4.0 mm posterior to the limbus. In all cases, scleral indentation-free total vitrectomy under triamcinolone acetonide visualization, additional panretinal photocoagulation, and direct photocoagulation for MA were performed if needed. After the above procedure, using a 27-gauge micro-forceps, internal limiting membrane (ILM) peeling of the lower half was performed within the range of papilla diameter 2 centered on the fovea, leaving the upper half for subsequent inverted ILM flap technique. Then, by grabbing the inner layer of the fovea using the ILM forceps, an iMH was created. The location of the fovea was identified from the preoperative fundus and optical coherence tomography (OCT) findings. The subfoveal HE was then flushed from the iMH with a balanced salt solution (BSS) as much as possible. In all cases, subretinal HE was yellowish and mostly diffused from the subretinal space to the vitreous cavity by spraying BSS. However, retroretinal adhesions of HE, such as to the lower part of the fovea in Case 2 and to the temporal lower lesion of the fovea in Case 3, were not partially released by BSS spray. We did not perform any more procedures because we were afraid of retinal damage due to excessive manipulations. Finally, the inverted ILM flap technique was performed using the upper half of the ILM that was left during the previous maneuver. At the end of the surgery, the eyes were flushed with 50 mL of 20% sulfur hexafluoride (SF_6) after the fluid-air exchange of the vitreous cavity. Intraocular pressure was checked by tactile

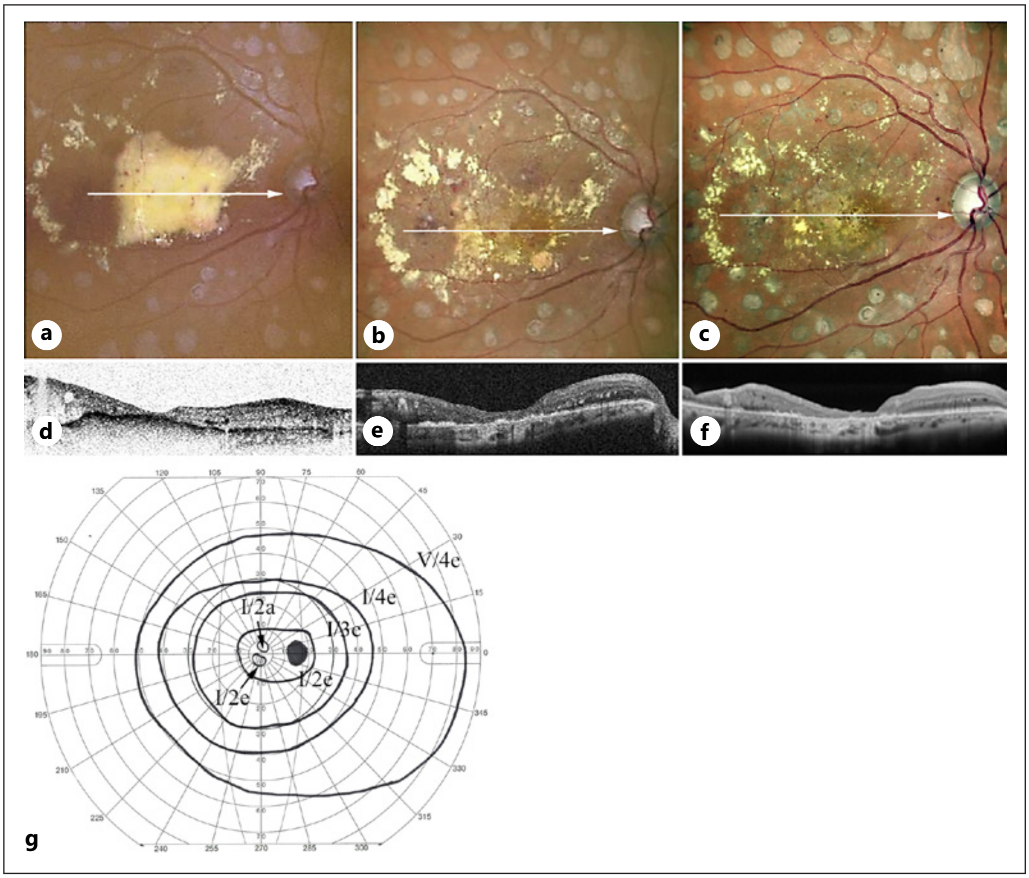

Fig. 1. Funduscopic findings revealed massive subfoveal HE deposits in the right eye at the first visit (**a**). OCT findings revealed a subretinal high reflective mass due to subfoveal HE, marked thinning of the foveal retinal thickness, and complete loss of the continuity of subfoveal ELM and EZ lines in the right eye (**d**). One month after surgery. Subfoveal HE decreased significantly immediately (**b**). There has been no recurrence of subfoveal HE (**c**). The discontinuity of ELM and EZ on OCT findings did not recover 1 month (**e**) and 6 months (**f**) after the surgery. On Goldmann perimetry findings at 6 months after the surgery, no apparent central scotoma due to surgical maneuver was detected (**g**).

examination. Finally, 40 mg of sub-Tenon's triamcinolone acetonide (Kenacort A-40®, Bristol-Myers Squibb, Japan) was injected, and antibiotic ointment was administered at the end of the surgical procedure.

Case 1

A 55-year-old woman with mental retardation presented after becoming aware of decreased visual acuity in both eyes. She had been treated for diabetes and DR. On blood examination, HbA1c was 7.2%. At the first visit, her best-corrected decimal visual acuity (BCVA) was 0.15 (Snellen equivalent [SE], 20/125) OD and 0.8 (SE, 20/25) OS. In the slit-lamp examination, no remarkable findings were observed in the anterior segment of both eyes. Funduscopic examination revealed multiple MAs at the temporal side of the fovea and massive subfoveal HE deposits in the right eye (Fig. 1a) and cystoid macular edema in the left eye. Panretinal photocoagulation for DR had already been performed in both eyes. OCT revealed a subretinal high reflective mass due to subfoveal HE, marked thinning of the foveal retinal thickness, and complete loss of the continuity of subfoveal external limiting membrane (ELM) and ellipsoid zone (EZ) lines in the right eye (Fig. 1d). Although the conventional treatments, including direct photocoagulation for capillary MAs, sub-Tenon's or intravitreal injections of triamcinolone acetonide, and intravitreal anti-VEGF administration, were thought to be effective treatment options, she experienced difficulty undergoing continuous outpatient treatment due to mental retardation. Thus, we performed PPV with the removal of subfoveal HE in her right eye to maintain her visual function (see online suppl. Video, clip 1; for all online suppl. material, see www.karger.com/doi/10.1159/000526150, which demonstrates the creation of iMH, removal of subfoveal HE, and inverted ILM flap technique in case 1). The details of the surgical procedure are listed above. After surgery, the iMH was successfully closed. Subfoveal HE decreased significantly immediately after surgery and then gradually (Fig. 1b). Although there has been no recurrence of subfoveal HE (Fig. 1c), the discontinuity of ELM and EZ on OCT findings did not recover during the follow-up period (Fig. 1e, f). Six months after the surgery, her BCVA has been improved to 0.7 (SE, 20/30–20/25), and no apparent central scotoma OD was detected on Goldmann perimetry (GP) (Fig. 1g).

Case 2

A 69-year-old man was referred for the treatment of visual disturbance due to DR in both eyes. He had no treatment history for the DR. His blood examination showed an HbA1c level of 10.7%. At the initial visit, BCVA was 0.5 (SE, 20/40) OD and 0.1 (SE, 20/200) OS. A fundus examination revealed a subfoveal thick HE and MAs at the temporal side of fovea OS (Fig. 2a). OCT findings revealed a subretinal high reflective mass caused by a subfoveal HE, a marked thinning of the foveal retinal thickness, and complete loss of the continuity of subfoveal ELM and EZ lines OS (Fig. 2d). In his left eye, GP revealed I/4e central scotoma (Fig. 2g). For his left eye, PPV with subfoveal HE removal was performed because the subfoveal photoreceptor layer was already severely damaged and subfoveal HE needed to be removed as soon as possible to keep his visual function. The details of the surgical procedure are mentioned above. After surgery, the iMH was successfully closed. The subfoveal HE subsided shortly after surgery (Fig. 2b) without recurrence during the 6-month follow-up period (Fig. 3c), although the subfoveal retinal pigment epithelium damage persisted and the ELM and EZ lines did not recover on OCT findings OD (Fig. 2e, f). His BCVA improved to 0.3 (SE, 20/60), and preoperative I/4e central scotoma detected on GP got smaller OD 6 months after the surgery (Fig. 2h).

Case 3

A 62-year-old man was referred for untreated DR in both eyes. The HbA1c level was 9.8% on his blood examination. At his first visit, BCVA was 0.04 (SE, 20/500) OD and 1.2 (SE, 20/16) OS. Fundus examination revealed subfoveal HE and MAs on the temporal side of the fovea OD (Fig. 3a). OCT findings showed a subretinal high reflective mass secondary to subfoveal HE, the thinning of the foveal retinal thickness, and destroyed outer layer structures OD (Fig. 3d). PPV with subfoveal HE removal through iMH was performed for his right eye as in cases 1 and 2. After surgery, the iMH was successfully closed (Fig. 3e). The subfoveal HE decreased gradually one (Fig. 3b) and 6 months after surgery (Fig. 3c), but the outer retinal layer structure did not recover on OCT findings compared to the preoperative findings (Fig. 3f). The BCVA improved to 0.15 (SE, 20/125), and the preoperative I/4e central scotoma detected on GP (Fig. 3g) got smaller 6 months after the surgery (Fig. 3h).

Discussion/Conclusion

Multidisciplinary treatment centered on anti-VEGF procedures has enabled treatment of subfoveal HE with good results [4, 7]. However, the management of patients who are resistant to treatment, those who are unable to attend outpatient clinics constantly, and those with

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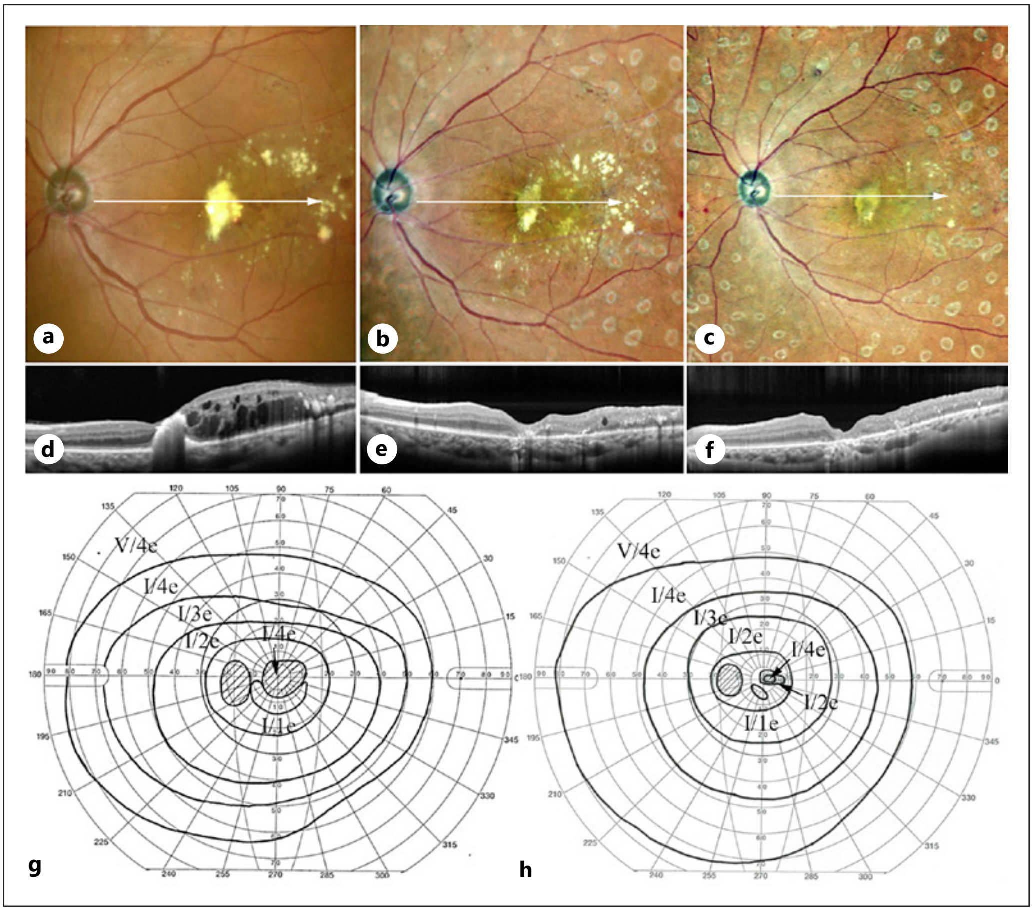

Fig. 2. Fundus examination revealed a subfoveal thick HE and MAs at the temporal side of fovea OS at the first visit (**a**). OCT findings revealed a subretinal high reflective mass caused by subfoveal HE, a marked thinning of the foveal retinal thickness, and complete loss of the continuity of subfoveal ELM and EZ lines OS (**d**). One month after surgery, the subfoveal HE subsided shortly (**b**). There was no recurrence of subfoveal HE 6 months after the surgery (**c**). The subfoveal retinal pigment epithelium damage persisted, and ELM and EZ lines did not recover on OCT findings 1 (**e**) and 6 (**f**) months after the surgery. Goldmann perimetry findings revealed I/4e central scotoma just before the surgery (**g**). Six months after the surgery, I/4e central scotoma got smaller (**h**).

already existent subfoveal HE is one of the current challenges, and the development of new treatments for such patients is currently desired.

In recent years, the usefulness of surgical treatment for subfoveal HE secondary to DM has been reported [8, 9]. PPV for subfoveal HE was first reported by Takagi et al. [8] in 1994, and its utility has been extensively reported. However, some reports showed that the benefits of surgery are short-lived, and there is a considerable number of cases in which visual acuity deteriorates in the long term [10]. In addition, this conventional technique requires the creation of an intentional retinal tear on the foveal temporal side, which does not resolve concerns over the appearance of paracentral scotoma. Further, the possibility of retinal damage exists since the forceps are inserted under the retina to grasp and extract the HE itself. Thus, the procedure requires experience and proficiency. In 2020, Kumagai et al. [9] reported that BSS was injected under the retina using a 38 G needle to intentionally create iMH, from which BSS was sprayed onto the subretinal HE to remove it, resulting in a significant improvement in corrected visual acuity. It is possible that this technique has an advantage over the previously

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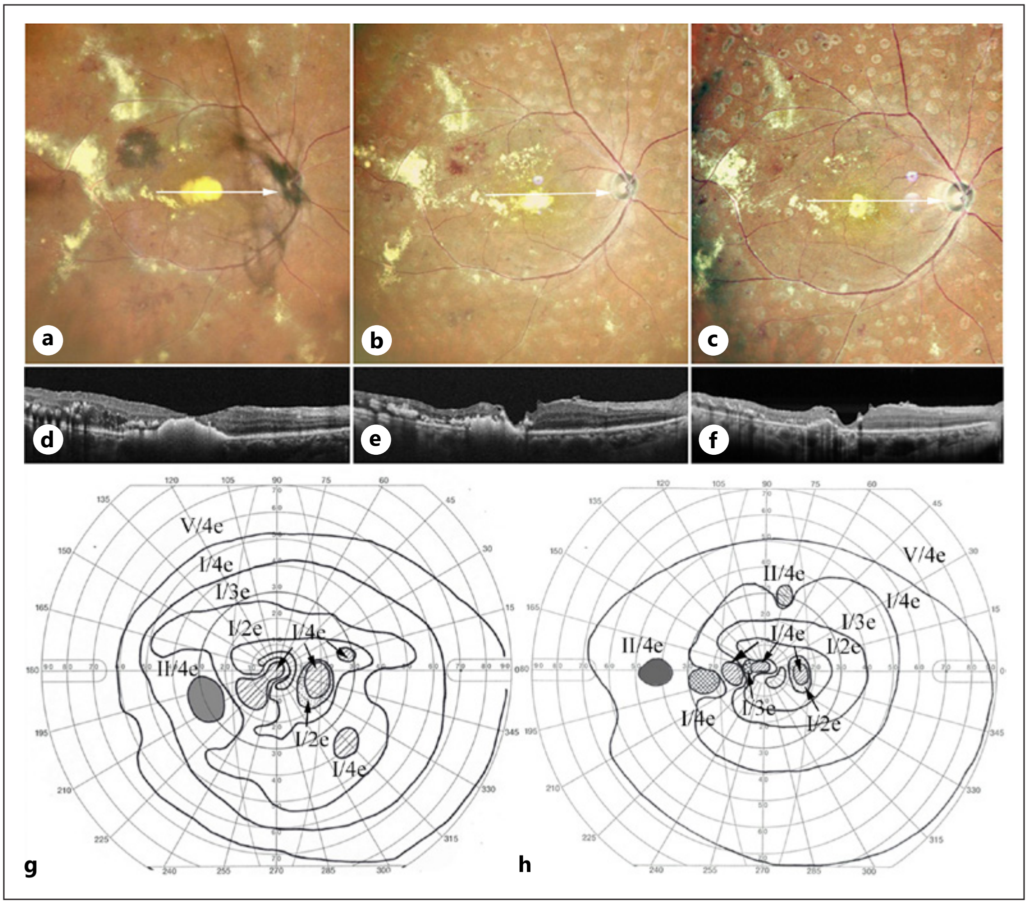

Fig. 3. Fundus examination revealed subfoveal HE and MAs on the temporal side of the fovea OD at the first visit (**a**). OCT findings showed a subretinal high reflective mass secondary to subfoveal HE, the thinning of the foveal retinal thickness, and destroyed outer layer structures OD (**d**). The subfoveal HE decreased gradually 1 month (**b**) and 6 months (**c**) after surgery. The outer retinal layer structure did not recover on OCT findings 1 month (**e**) and 6 months (**f**) after surgery. I/4e central scotoma was detected on Goldmann perimetry preoperatively (**g**). It got smaller 6 months after the surgery (**h**).

mentioned conventional surgical techniques, in which no paracentral scotoma appears. In our cases, the subfoveal HE was thick, making it unclear whether the BSS injection could cause an iMH. Therefore, the inner layer of fovea was grasped directly to create an iMH. As a result, corrected visual acuity improved, and no central scotoma occurred; rather, the preoperative scotoma diminished. Thus, this method may have great advantages in terms of preventing the occurrence of paracentral scotoma, in both the method of injecting BSS and the method of directly grasping the fovea. In contrast, there is a concern that the MH may persist when it is intentionally created. To prevent the persistence of MH, we used a combination of the inverted ILM flap technique [11] and closed the MH completely in all cases. However, in the report by Kumagai et al. [9], the inverted ILM flap technique was not used, and MH closure was obtained in all cases. In the future, it will be necessary to consider a large number of cases to assess whether or not the combination of inverted ILM flap technique is recommended.

In addition to this technique, PPV, ILM peeling, direct retinal photocoagulation, and sub-Tenon's triamcinolone injection were performed in our cases, and we believe that all procedures worked effectively. Thus, being able to perform multiple procedures simultaneously during the same surgery is considered one of the advantages of PPV.

Undoubtedly, patients with DM should be prioritized for outpatient treatments such as anti-VEGF administration, direct photocoagulation, and triamcinolone sub-Tenon's or intravitreal injections. Therefore, the optimal timing for surgical subfoveal HE removal is still under debate. In previous reports, the Early Treatment Diabetic Retinopathy Study classification based on a set of standard photographs was used for categorical assessment of HE [6]. Based on these standard photographs, the area of HE was graded as definite (>0–0.1 mm^2), obvious (>0.1–0.5 mm^2), moderate (>0.5–2.5 mm^2), or severe (>2.5 mm^2). In the RISE and RIDE study phase III trial, in which one eye per patient was randomized to monthly sham injections or monthly intravitreal injections of 0.3 or 0.5 mg ranibizumab through month 24, HE area improved in most eyes, with a higher proportion of patients demonstrating a 2-step improvement in the ranibizumab groups compared with the sham group. However, even in the 0.5 mg ranibizumab group, the 2-step improvement of HE in obvious, moderate, and severe categories were 63%, 34%, and 12.5%, respectively [6]. This finding suggests that the effect to decrease HE is up to the base level of HE sizes even after the anti-VEGF therapy. Moreover, a previous report suggested that the surgical excision of plaque-like (larger than 1.3 disc diameter) subfoveal HE resulted in a better anatomical and functional outcome compared with the observation group [12]. Thus, the indication for surgical removal of subfoveal HE may be a giant HE, measuring more than 1/2 to 1-disc diameter of HE. However, when it is economically and physically difficult for the patient to receive ambulatory treatment and if the patient has an existing disease that may complicate their health further, surgical treatment should be considered a viable option. In conclusion, removal of HE from iMH can be one of the treatment options for patients who cannot receive conventional treatments centered on anti-VEGF therapy and those who need immediate HE removal because of already existing severe photoreceptor damage.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board in Mahoshi Hospital (approved on October 10, 2020) and adhered to the tenets of the World Medical Association Declaration of Helsinki. No written informed consent has been created, but verbal informed consent was obtained from all patients and the proxy decision maker (identity underwriter) for patient 1 for publication of the details of their medical case and any accompanying images, which was included in the medical records. For patient 1, although the patient had mental retardation, she could make her own decisions and her surgical consent was also given by her own signature. Therefore, verbal informed consent could be obtained from the patient herself. However, just in case, we obtained the consent of the hospital facility staff who was the proxy decision maker. This consent procedure was reviewed and approved by the institutional review board in Mahoshi Hospital (approved on October 10, 2020). Moreover, this report does not contain any personal information that could lead to the identification of the patient in accordance with the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Hisanori Imai designed the concept of this work. Yukako Iwane, Hiroko Yamada, and Hisanori Imai drafted this manuscript. Hiroko Yamada, Yasuyuki Sotani, Mariko Oishi, and Makoto Nakamura critically reviewed the manuscript. Yukako Iwane, Hisanori Imai, Hiroko Yamada, Yasuyuki Sotani, Mariko Oishi, and Makoto Nakamura read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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