

Surgical Management of Massive Submacular Hemorrhage

Vitrectomy and subretinal rtPA are options to be considered.

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Massive submacular hemorrhage (SMH) is a potentially devastating complication of certain retinal diseases, particularly neovascular age-related macular degeneration (AMD) and retinal arterial macroaneurysms (RAMs). Natural history studies have demonstrated relatively poor initial visual acuities leading to variable outcomes. Although some patients were observed to improve or stabilize spontaneously, most patients experienced further decline in vision with time. Poor prognostic factors include the presence of subretinal neovascularization, an underlying diagnosis of AMD, and significant hemorrhagic elevation of the retina. The pathophysiology of accumulated blood in the subretinal space is thought to involve impairment of nutrient exchange between the retinal pigment epithelium (RPE) and the outer retina, mechanical damage to photoreceptors during clot contraction, and possibly iron toxicity. There are a number of treatment strategies for massive SMH, but there are no formal guidelines regarding the optimal management. This article discusses the evolution of therapies for massive SMH and studies that have guided current therapeutic strategies for large or massive SMH.

CASE EXAMPLE

A 77 year-old man presented following the new onset of a “blob” in the central vision of his right eye. He had already lost central vision to cicatricial complications of AMD in his left eye. Review of his previous records revealed that his right eye was 20/20 just 3 months prior to the onset of the current problem and he had a diagnosis of stable dry AMD.

On examination, he demonstrated a visual acuity of 20/150 in the right eye and 20/800 in the left. His poste-

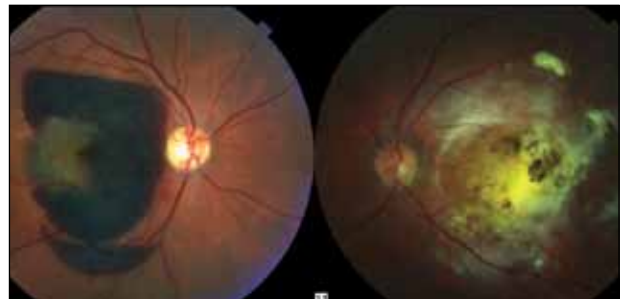


Figure 1. Massive SMH, right eye. Fibrotic scar, left eye.

rior segment examination revealed a massive submacular hemorrhage in the right eye and inactive fibrotic macular scarring in the left eye (Figure 1). Fluorescein angiography (FA) confirmed the presence of minimally classic choroidal neovascularization (CNV [Figure 2]). Thick subretinal hemorrhage was seen on optical coherence tomography (OCT) examination (Figure 3).

Given the extent of the hemorrhage in this patient's functional eye, he was offered surgical displacement of the submacular blood, which he underwent 7 days following the event.

TECHNIQUE

Pars plana vitrectomy was performed with 25-gauge instrumentation using the Accurus vitrectomy system (Alcon Laboratories Inc.). Following removal of vitreous, a single port was enlarged with a microvitrectomy blade to accommodate 20-gauge instrumentation

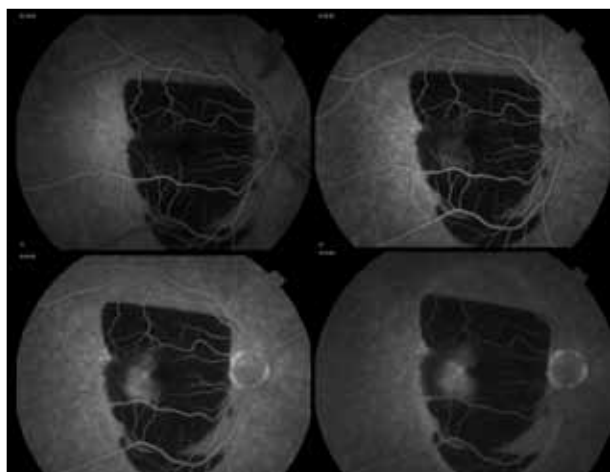


Figure 2. FA with minimally classic choroidal neovascularization.

for the subretinal cannula (de Juan 41-gauge subretinal cannula, Bausch + Lomb). Recombinant tissue plasminogen activator (rtPA) was utilized to facilitate liquefaction of the subretinal clot. Specifically, alteplase was reconstituted in 0.9% normal saline for a concentration of 10 µg per 0.1 cc inside a 10-cc syringe. The syringe was then connected to the automated viscous fluid infusion modality on the Accurus system, and rtPA was advanced through the syringe/cannula prior to entering the eye. The flow rate is slowly titrated upward until observation of slow and steady drops, almost but not completely achieving a continuous stream at approximately 16 mm Hg syringe infusion pressure. Of note, attention was paid to thorough removal of peripheral vitreous gel near the sclerotomy site to preserve the integrity of the delicate microcannula tip. The cannula was then carefully introduced through the enlarged port and inserted directly into the subretinal clot in a transretinal approach away from the foveal center. The reconstituted rtPA solution was then delivered to the subretinal space, creating a bleb encompassing the clot. Care was taken, under high magnification visualization, to avoid entry of the rtPA into the sub-RPE space. Once the macular region of the retina had a bleb of subretinal rtPA that extended to the edges of the massive SRH and just beyond, the cannula was removed from the subretinal space. Finally, a complete fluid-gas exchange with 20% SF₆ was

carried out. Postoperatively, the patient was asked to maintain face-down positioning for 3 days, although only 1 day of positioning is probably necessary.

CASE FOLLOW-UP

At the third postoperative week, the patient's vision had improved to 20/70, and the majority of the subretinal blood had been displaced inferiorly revealing an extrafoveal RPE tear (Figure 4). OCT demonstrated the presence of a pigment epithelial detachment with subretinal and intraretinal fluid (Figure 5). At this visit, he underwent the first of a series of monthly intravitreal injections with anti-VEGF agents.

By the third postoperative month, his vision had improved to 20/40 with interval improvement on fundus imaging appearance, but there was still fluid present on OCT examination (Figures 5 and 6). Serial anti-VEGF injections were continued approximately every 4 to 6 weeks, and over the course of the next 5 years the patient's vision and subsequent imaging studies have shown improvement (Figures 7-9). Despite the initial guarded prognosis, the patient has improved dramatically and his vision is maintained currently at the 20/20 level.

DISCUSSION

In the early 1980s, Glatt and Machemer¹ published their work in an animal model of the hemorrhagic stage of AMD. They injected autologous blood into the subretinal space of rabbits and then studied the effects using ophthalmoscopy and light and electron microscopy. Early photoreceptor edema was observed within 24 hours, and severe damage to the outer nuclear layer was seen at 7 days. At 2 weeks after injection, they found the photoreceptor and outer nuclear layers to be absent. It was concluded that a hemorrhagic barrier between the RPE and outer retina severely impairs metabolic exchange and also that tractional forces exerted by the clot on the photoreceptors is detrimental.

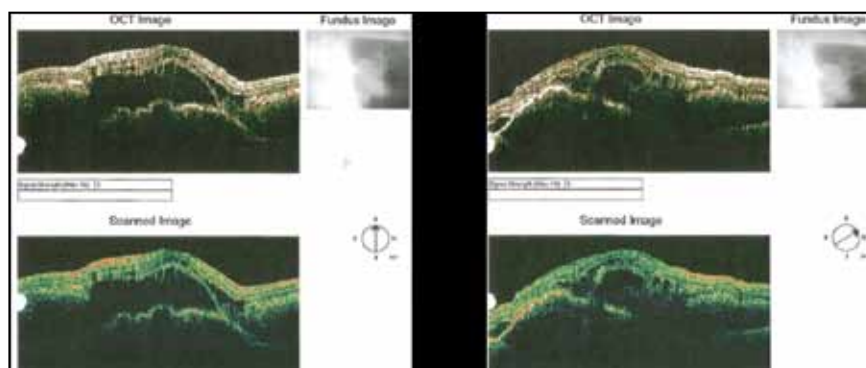


Figure 3. Stratus OCT with thick subretinal hemorrhage.

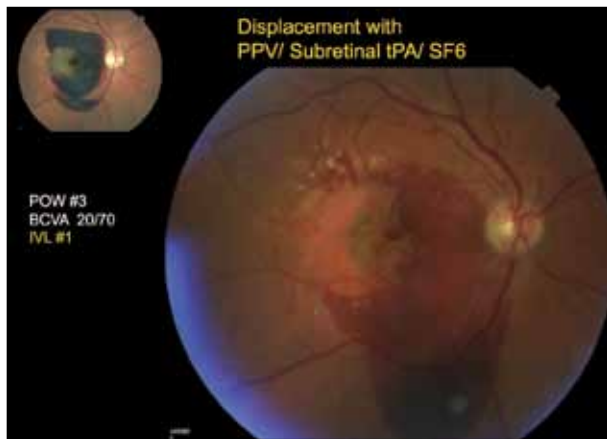


Figure 4. Fundus appearance, 3 weeks postoperative, vision 20/70.

tal. Furthermore, they postulated that iron toxicity to the retina also contributed to the destruction that was observed. The first case publications of surgical evacuation of subretinal hemorrhage were published later in the 1980s with variable outcomes.^{2,3} Shortly thereafter, Toth et al^{4,5} confirmed the importance of the mechanical forces in a cat model, and the idea of using subretinal rtTPA in facilitating removal was introduced in animal studies.⁵⁻⁸ The adjunctive use of rtTPA in submacular surgery grew in the 1990s.

Interest in the surgical management of SMH grew as more case series were published. However, these early attempts resulted in a wide range of outcomes, and it also became recognized that a subset of patients with subretinal hemorrhage may experience significant improvement without intervention, particularly those without subretinal neovascular membrane, AMD, or large or thick SMH.⁹ To help better define the role of surgery in SMH associated with choroidal or subretinal neovascular membrane, the Submacular Macular Surgery Trial (SST)¹⁰ was initiated as a prospective, randomized controlled trial in the late 1990s. Specifically, SST Group B investigated hemorrhagic neovascular complexes in AMD. The study included choroidal neovascular (CNV) membrane lesions with hemorrhage occupying at least 50% of the lesion and total lesion size of greater than 3.5 disc areas. The study did not address thick or massive SMHs as a separate subgroup. The results, published in 2004, demonstrated no benefit to surgery relative to observation alone. Furthermore, rhegmatogenous retinal detachments (RRDs) occurred in 16% of the surgical group, with about half of those RRDs complicated by PVR. In subgroup analysis, however, the surgical group had a lower risk of severe vision loss when compared with

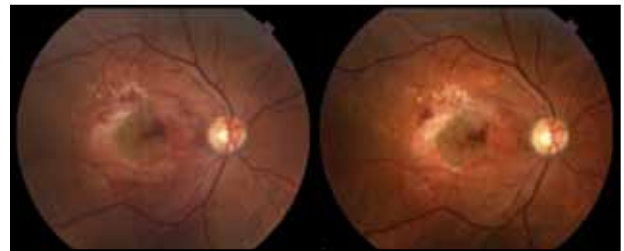


Figure 5. Fundus appearance, 3 months (right) and 4 months (left) postoperative.

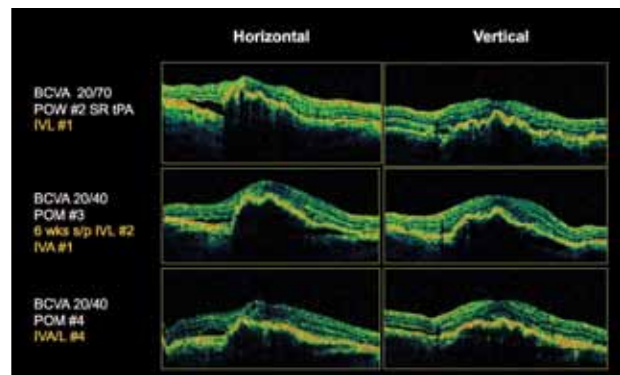


Figure 6. SD-OCT, postoperative, shows presence of fluid.

the observation group (21% vs 36%; $P = .004$). Other surgical approaches, such as macular translocation and RPE patch surgery, have also been proposed with variable success but minimal widespread acceptance at the current time.

Endeavoring to avoid collateral retinal damage and other potential complications arising from surgical evacuation of SMH, less invasive options have been pursued. In 1996, Heriot¹¹ proposed an alternative in-office procedure to displace the SMH from the macula employing intravitreal rtPA in combination with gas displacement and face-down positioning. Subsequent published series of this technique for large SMH have shown positive results with successful displacement in 71 to 100% and with vision improvement of 2 lines or greater in 64 to 69%.¹²⁻¹⁴ Still, some concerns remain about possible further damage to photoreceptors when displacing without adequate clot liquefaction and whether intravitreal rtPA truly penetrates to the clot in the subretinal space. These issues have contributed to the development of a hybrid approach involving pars plana vitrectomy for delivery of subretinal rtTPA and fluid-gas exchange followed by face down positioning. Positive results have been reported with successful SMH displacement in 86 to 100% and stabilization or improvement in 82 to 90% of patients within the first 3 to 6 months.^{15,16}



Figure 7. Fundus appearance, 3 years postoperative, vision 20/30.

In addition to advances in surgical technique, the more recent advent of effective therapies for choroidal or subretinal neovascular membrane has offered a promising new approach in management of SMH. Whereas traditional submacular surgical maneuvers tried to extract the CNV and hemorrhage, they failed to, on average, provide the type of optimal anatomic and visual outcomes that we are now accustomed to with anti-VEGF therapy. Photodynamic therapy has been noted to slow the progression of visual loss in SMH, but, more prominently, anti-VEGF therapy is emerging in recent years as a key treatment modality for hemorrhage from choroidal or subretinal neovascular membrane. Furthermore, a few recent studies have even described bevacizumab (Avastin, Genentech) monotherapy¹⁷ and ranibizumab (Lucentis, Genentech) monotherapy^{18,19} in the management of SMHs, some of which were large or thick.

An important factor that hinders comparison in the literature of the different approaches is a relative lack of standardization and quantification of the severity or extent of subfoveal and juxtafoveal hemorrhage, which is a key factor when deciding if a patient should undergo an attempt at displacement. There should be a significant elevation of the fovea itself by the subretinal hemorrhage, and the macular hemorrhage should be unequivocally “massive” in its qualitative assessment. It is likely inappropriate to offer this surgery for patients who have just a moderate SMH or who have a massive SMH that spares the fovea itself. Additionally, anterior-

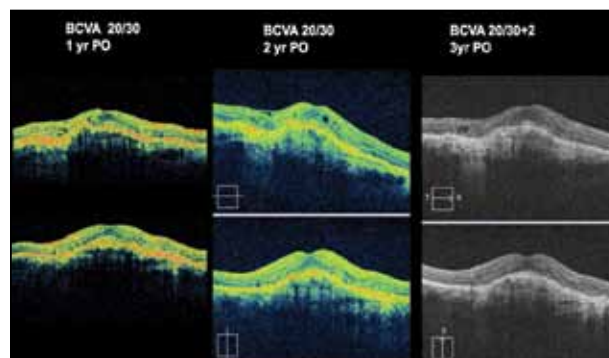


Figure 8. SD-OCT, 1, 2, 3 years postoperative.



Figure 9. Fundus appearance, at presentation (right) and at 5 years (left).

posterior location of the hemorrhage vis-a-vis the neural retina and underlying RPE as seen on preoperative OCT may also prove to be important, as sub-RPE hemorrhage may not be as amenable to surgery as is blood in a subretinal location above the RPE.

One limitation of the use of vitrectomy and subretinal rtPA for the management of massive SMH is that subsequently delivered anti-VEGF agents may have a decreased intraocular half-life in the vitrectomized eye. It may therefore be difficult to extend dosing of these agents much beyond 4 weeks in these patients.

CONCLUSIONS

The management of SMH associated with CNV or AMD has changed considerably over the past 25 years. At this time, we have the great privilege to offer patients treatments that routinely prevent further loss of function and, in most cases, improve what would otherwise be a devastating event. Anti-VEGF therapy remains the standard of care for choroidal or subretinal neovascular membrane, and it has become evident that it plays a crucial role in the management of SMH arising from neovascularization. Displacement of SMH remains an important option in a subset of patients with larger or thicker accumulations of blood. We await future studies to help clarify the relative

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efficacies of the different approaches and combinations and which particular subsets of patients stand to benefit the most. ■

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