Different approaches in the management of macular hemorrhage: Case reports and a literature review

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Abstract

Introduction

Macular hemorrhages result in a sudden and profound loss of vision. The primary treatment modalities include observation, intravitreal injection of antiangiogenic drugs, neodymium-doped yttrium aluminum garnet laser hialoidotomy, intravitreal injection of gas with or without tissue plasminogen activator, as monotherapy or combined with surgery. In this paper, we report four cases of macular hemorrhages of different causes treated with different approaches, and we review the literature in this regard.

Case presentation

All four patients presented different causes of macular hemorrhage. The first case had a preretinal hemorrhage due to a Valsalva retinopathy and was treated with surgery. Case 2 had a multilevel macular hemorrhage due to a rupture of a retinal arteriolar macroaneurysm and was treated with pneumatic displacement, laser, and intravitreal ranibizumab. Case 3 presented an extensive subretinal hemorrhage due to a choroidal rupture after high-energy ocular trauma that was also successfully treated with surgery. The last case was a preretinal hemorrhage due to diabetic retinopathy managed with neodymium-doped yttrium aluminum garnet laser. Different treatment approaches were successfully performed in all cases with good outcomes.

Conclusion

There is an extensive range of options available for the management of macular hemorrhages, and the best option depends on the characteristics of each particular case. Proper and timely management of these diseases can achieve an excellent visual outcome, especially if the location of the hemorrhage is preretinal.

Main messages

- Caused by alterations to retinal or choroidal circulation, macular hemorrhage is an accumulation of blood in the macular area.
- Subretinal hemorrhages have a worse prognosis, due to the toxicity of the blood on the photoreceptors and the retinal cells.
- Taking into consideration the time, mechanism, and location of the hemorrhage, appropriate and timely management of these entities can achieve an adequate visual outcome.
- Surgery is not always the first option for the management of macular hemorrhages as each case must be individualized.

Introduction

Macular hemorrhages are accumulations of blood in the macular area, and originate in alterations of the retinal or choroidal circulation. Depending on their location, they may be preretinal (sub-internal limiting membrane or subhyaloid), subretinal, subretinal pigment epithelium, mixed (subretinal and sub-retinal pigment epithelium), and may be located in more than two layers[1]. This condition is associated with a wide variety of diseases, including age-related macular degeneration, retinal arteriolar macroaneurysm, pathological myopia or ocular trauma[2]. The natural history, when left untreated, will depend on the location of the hemorrhage, with subretinal hemorrhages having the worst prognosis because the blood itself is toxic to the photoreceptors and retina[3].

Treatment options are broad and depend on the etiology and the anatomical location of the lesion. Depending on the case, we can use: intravitreal anti-vascular endothelial growth factor drugs; subretinal or intravitreal tissue plasminogen activators; pneumatic displacement with gas; laser treatment; or pars plana vitrectomy with or without the use of intravitreal gas[1,4-7].

We present four cases of macular hemorrhages with different therapeutic approaches. In addition, we conducted a literature review, highlighting the importance of an accurate diagnosis according to the anatomical location, time of the disease, and factors related to management and visual prognosis.

Case 1

A 43-year-old healthy woman presented sudden and non-painful loss of vision, with 16 hours of evolution, in the left eye after intense physical activity (Valsalva maneuver) while trying to lift a heavy object. She reported that a large spot was blocking her central vision. After examination, best-corrected visual acuity was 20/20 and counting fingers in the right and left eye respectively. Anterior segment examination was normal. Dilated fundus examination of the left eye revealed a large premacular hemorrhage (three-disc diameters in area) that extended through the macular area, obscuring macular details with an additional level next to the inferior arcade (Figure 1A). Fluorescein angiography of the retina did not reveal areas of leakage (Figure 1B), and optical coherence tomography showed a dense hyperreflective material (blood) on the subhyaloid and sub-internal limiting membrane area (Figure 1C). Clinical and laboratory tests were performed in which systemic pathologies (diabetes mellitus, arterial hypertension, dyslipidemia, among others) and blood dyscrasias (anemia, thrombocytopenia, leukopenia, or coagulation alterations) were ruled out. The clinical diagnosis of Valsalva retinopathy was made. After the third week of follow-up, there was no improvement in visual acuity, and a 25-Gauge pars plana vitrectomy was performed. While performing vitrectomy, posterior vitreous detachment and internal limiting membrane peeling was conducted. During the peeling, the localization (sub-internal limiting membrane) of the lesion was confirmed, thus releasing the hemorrhage (Figure 1D). The best corrected visual acuity was 20/20 at one and twelve months after the surgery (Figures 1E and 1F).

Case 2

A hypertensive 71-year-old woman presented at the retina service with a sudden onset of painless vision loss in the left eye with 8 days of evolution. Ocular history was unremarkable. The best corrected visual acuity was 20/50 in the right eye and counting fingers in the left eye. Anterior segment examination showed a mild sclerosis of the lens on both eyes. Left eye fundus revealed a dome-shaped central premacular hemorrhage, with well-defined edges and foveal involvement, surrounded by a subretinal hemorrhage (with an area of 3.5 disc in diameter), associated with a premacular hemorrhage (Figure 2A). Fluorescein angiography of the retina showed a large hypofluorescent area due to retinal and choroidal blockage, without any areas of leakage (Figure 2B). Optical coherence tomography showed dense hyperreflective material (blood) at several levels (subhyaloid, sub-internal limiting membrane, and subretinal) of the retina (Figures 2C and 2D). Two weeks later, a pneumatic displacement using an intravitreal injection of sulfur hexafluoride (SF6) gas at 100% with inmediate prone position was performed. The position was maintained for 5 days. On the day following the procedure she developed vitreous hemorrhage, but on the ninth day after the procedure, visual acuity improved to 20/400, subretinal hemorrhage was displaced outside the fovea, and a rounded vascular lesion compatible with retinal arteriolar macroaneurysm on the superior temporal arcade was evident. Laser was applied directly, and surrounding the retinal lesion, using a 532 nanometer laser (OcuLight® TX, Iridex Corporation, Mountain View, CA, United States). Additionally, intravitreal Ranibizumab (Lucentis ©, Genentech, South San Francisco, CA) was injected one week after completing three monthly doses. At four months, the best corrected visual acuity was 20/40, with complete resolution to the hemorrhages. A fibrotic (whitish) lesion with a hyperpigmented ring over the superior temporal arcade was evident (Figures 2E and 2F).

Case 3

A healthy 56-year-old female patient came to us reporting a sudden decrease in visual acuity on the right eye, secondary to a high-energy closed eye trauma. The trauma was caused by a whiplash mechanism due to a loose wire from a distance of two meters in height. Her visual acuity was hand movement in the right eye and 20/25 in the left eye. The intraocular pressure was normal and the anterior segment evaluation showed 360 degree hyposphagma, without any others alterations. On fundus examination, extensive subretinal hemorrhage was evident obscuring all the macular area (Figure 3A). Optical coherence tomography displayed the presence of hyperreflective material (blood) on the subretinal area. (Figure 3B). Pneumatic displacement with 100% sulfur hexafluoride (SF6) gas and prone position was performed on the same day. However, on the sixth day of the procedure, vitreous hemorrhage was evident and visual acuity did not improve. A 25-Gauge pars plana vitrectomy was performed with 20% sulfur hexafluoride gas used as endotamponade associated with face-down positioning. Two months later, visual acuity improved to 20/400, and a fundus exam exhibited a choroidal rupture with a reduction of the hemorrhage of more than 50%, maintaining these findings at two years of follow-up (Figure 3C). Optical coherence tomography showed subretinal hyperreflective material with posterior optic shadow, corresponding to subretinal fibrosis (Figure 3D).

Case 4

Due to proliferative diabetic retinopathy from a year prior, a 54-year-old diabetic and hypertensive female, with previous history of having received two sessions of panretinal photocoagulation in both eyes, came to the eye clinic reporting a painless loss of central vision in

her left eye seven days prior. Best corrected visual acuity was 20/30 in the right eye and counting fingers in the left eye. There was no afferent pupillary defect and anterior segment examination was normal with mild nuclear sclerosis of the lens. Dilated fundus examinations revealed a proliferative diabetic retinopathy in both eyes with an extensive preretinal, sharply demarcated, dome-shaped hemorrhage at the posterior pole of the left eye, covering most of the macula including the fovea (Figure 4A). Immediate supplemental panretinal photocoagulation was applied in both eyes and hyaloidotomy/membranotomy was performed on the same day using a Neodymium-doped yttrium aluminum garnet ($Y_3Al_5O_{12}$) laser (Alcon 3000LE® neodymium-doped yttrium aluminum garnet laser, Alcon, Fort Worth, TX), with a Goldmann three-mirror contact lens (Volk Optical Inc., Mentor, OH, United States) and a power of 6.2 millijoules to create an opening in the posterior hyaloid near the lower edge of the hemorrhage (Figure 4B). Twenty days after the procedure, the best corrected visual acuity improved to 20/100. The fundus examination showed mild inferior vitreous hemorrhage and almost complete resolution of preretinal hemorrhage (Figure 4C).

Discussion

Four patients with different etiologies of macular hemorrhages, which were managed very differently, were reported here. The first case presented a preretinal hemorrhage due to Valsalva retinopathy, and was treated with vitrectomy and internal limiting membrane peeling. This reflects the positive visual outcomes these patients can achieve through timely surgery. In case 2, the multilevel hemorrhage, associated with the clinical context, made us suspect a ruptured retinal arteriolar macroaneurysm, which was confirmed after blood displacement with gas. Despite having some of the hemorrhage on the subretinal space, it was timely management, in this case, that ensured a good final visual acuity. On the other hand, despite the partial improvement of vision with the appropriate treatment, case 3 did not go as well, which corroborates with the fact that when the lesion is on the subretinal area, affects the fovea, and there is another associated lesion (such as the choroidal rupture due to high energy ocular trauma presented here) the visual prognosis is more poor. In the last case, we observed the resolution of a preretinal hemorrhage due to proliferative diabetic retinopathy treated with neodymium-doped yttrium aluminium garnet laser hyaloidotomy/membranotomy, which successfully drained the hemorrhage since it was performed during the first days of the presentation[8].

Bopp and Mirshahi proposed a classification system for macular hemorrhages called FLATCAPS (Foveal Involvement, Retinal Layers, Age/Duration, Thickness, Cause/Pathogenesis, Size)[1], in which they assessed:

- F: Foveal involvement, as absent (F0) or present (F1).
- L: Retinal layers involved, being able to be of preretinal location (L0), subretinal (L1), sub-retinal pigmentary epithelium (L2), mixed subretinal and sub-retinal pigmentary epithelium (L3) or in more than two retinal layers (L4).
- A: Age/Duration, up to seven days (A0), from 8 to 14 days (A1) or > 14 days (A2).
- T: Thickness, < 500 micrometers (T0), 500 - 1000 micrometers (T1) or > 1000 micrometers (T2).
- CAP: Cause/Pathogenesis, non-neovascular (P0), choroidal neovascular (P1) or retinal neovascular (P2).
- S: Lesion size, < 1 disc area (S0), 1 to 5 disc areas (S1), > 5 disc areas and up to the arcades (S2) or a massive hemorrhage exceeding the arcades (S3).

As we will detail in the following paragraphs, this classification helps the ophthalmologist to summarize the most relevant information of the case, guides in the identification of the background pathology, in management planning, and in the prognosis of this condition.

Preretinal hemorrhages

They usually occur in vascular diseases of the retina, such as retinal arteriolar macroaneurysms, proliferative diabetic retinopathy[1], retinal venous occlusions or, more rarely, by Valsalva retinopathy (peripheral capillary rupture due to an increased intrathoracic or intra-abdominal pressure secondary to intense physical activity, vomiting, cough, constipation, pregnancy or sexual activity)[9], or by Terson syndrome (intraocular hemorrhage associated with subarachnoid hemorrhage and increased intracranial pressure; premacular hemorrhages are present in up to 39% of cases)[10]. Other causes include hematological disorders (aplastic anemia or leukemia), eye trauma, or shaken baby syndrome[2,3,10,11].

Preretinal hemorrhages can be located under the internal limiting membrane (dome-shaped, well-defined, associated with glistening light reflex reflected from its surface overlying the hemorrhage) or subhyaloid hemorrhages (associated with a level limiting the hemorrhage and movement downwards with the change of position of the patient's head), although often both are difficult to distinguish clinically even with imaging studies[11]. Preretinal hemorrhages usually have a good visual prognosis[11].

Several techniques have been described to treat premacular hemorrhages. These include observation, especially for hemorrhages of less than one disc area, which tend to be resolved spontaneously over a short period of time[12]. However, in dense and large hemorrhages, spontaneous resolution may take months and may generate permanent visual damage due to macular pigmentary changes, epiretinal membrane formation, macular holes or toxic damage due to permanent contact with hemoglobin and/or iron[9]. Neodymium-doped yttrium aluminium garnet laser membranotomy is useful on recent (up to three weeks) non-coagulated and non-dense macular hemorrhages[8], as shown in our case 4 (one week of evolution). This allows the drainage of hemorrhage into the vitreous cavity, facilitating the absorption of blood cells and improving vision by clearing the obstructed macular area[2,8,13], although it can present complications such as formation of macular holes, epiretinal membrane, persistence of premacular cavity or retinal detachment[11], which tends to be more frequent when the hemorrhage is sub-internal limiting membrane[13].

Pars plana vitrectomy may be more effective in cases where a dense premacular hemorrhage with insufficient spontaneous resorption is present, such as the one presented in the first case (without improvement after three weeks of follow-up), also allowing internal limiting membrane peeling and confirmation of the location of sub-internal limiting membrane hemorrhage. It may a have a better visual outcome, like our case, achieving 20/20 at the first month of surgery[11,12].

Subretinal hemorrhages

The majority are produced by choroidal neovascularization, 90% of these are secondary to age-related macular degeneration. Other less

common causes include retinal angiomatous proliferation, polypoidal choroidal vasculopathy and, more rarely, myopic or causes related to trauma[1]. Up to 10% of retinal arteriolar macroaneurysms present with subretinal hemorrhages[1] which are not associated with choroidal neovascularization and have variable clinical presentations, being able to present multi-level macular hemorrhages (subretinal and preretinal simultaneously in 40% of cases) as presented in case 2, and even vitreous hemorrhage (in 10%)[14,15].

It is important to remember that subretinal hemorrhages have the worst prognosis due to the potential damage to photoreceptors and retinal cells. Experimental studies have shown that the damage is irreversible in the retina and can occur as soon as 24 hours after the onset of bleeding[16]. In general, subretinal hemorrhages resolve spontaneously in an average of 6 to 8 months, eventually leading to the formation of a macular scar, atrophy or retinal pigment epithelium rips.

The most important mechanisms related to retinal damage are the toxicity from blood iron, the mechanical barrier of the clot, the retraction of the clot, and the shearing of photoreceptors, as well as damage to the cells of the retinal pigment epithelium[16]. If left untreated, the visual prognosis is severe, achieving a best corrected visual acuity of 20/200 or better in only 11% of cases at two years[17]. This is corroborated by case number 3, which is also associated with macular choroidal rupture, in which a visual acuity of 20/400 was achieved, as being the worst visual acuity among all our cases presented.

Management can be performed by observation or intervention (with or without vitrectomy). The treatment options reported include:

1. Intravitreal injection of anti-vascular endothelial growth factor drugs[18-20].
2. Pneumatic displacement with or without tissue plasminogen activator[7].
3. Subretinal injection of tissue plasminogen activator with gas[21,22], with perfluorocarbon liquids[23] or with hemorrhage drainage[24].
4. Vitrectomy and removal of the clot or the subretinal neovascularization, if present[25].
5. Photodynamic therapy.
6. Macular translocation.

These strategies have been used alone, in combination, at the same time, or sequentially. Several studies suggest that the use of intravitreal anti-vascular endothelial growth factor drugs alone (bevacizumab or ranibizumab) offer moderate visual gains in patients with submacular hemorrhages[26,27]. In a literature review of 122 patients treated with ranibizumab for subretinal hemorrhages due to choroidal neovascularization secondary to age-related macular degeneration, the median of the best corrected initial visual acuity was 20/153, improving to 20/100 after treatment[19]. These substances can also be used in combination with subretinal tissue plasminogen activator, expandable gas and/or vitrectomy. Reports evaluating the use of gas in combination with intravitreal anti-vascular endothelial growth factor drugs showed complete or partial displacement in 76% (22 of 29 patients) of cases, achieving a visual improvement of 20/200 or better in 66% patients (19/29)[19,28,29].

Other authors report the use of vitrectomy combined with subretinal or intravitreal tissue plasminogen activator and subsequent intravitreal bevacizumab, in patients with submacular hemorrhage due to age-related macular degeneration. This procedure achieved a total clot displacement in the 15 patients presented in the report, with a mean visual acuity gain of two or more lines of the Early Treatment Diabetic Retinopathy Study in 14 patients (93%)[19,22,30,31]. In cases where retinal arteriolar macroaneurysms is present, anti-vascular endothelial growth factor drugs have some potential because can achieve a faster resolution and can be used alone or in combination with laser treatment, with monthly regimes (from one to three intravitreal injections spaced by a month between them)[32-34].

Pneumatic displacement using only gas, according to several reports, has better visual outcomes when compared to the natural history of submacular hemorrhage, improving the best corrected visual acuity from 20/726 initial to 20/324 final[4,35,36].

The tissue plasminogen activator has two synergistic effects: enzyme-induced lysis of the clot and the mechanical displacement of liquefied blood by the gas bubble. Because it is a biological drug, the tissue plasminogen activator must be kept at low temperatures; its intraocular dose is not well established but it seems that 10 to 50 micrograms may be safe. However, some animal studies report high toxicity[37]. The safety of the drug is discussed since it is not manufactured for intraocular use. In addition to the retinal toxicity (atrophic changes, electroretinogram abnormalities and exudative retinal detachment) and recurrence of the neovascular membrane[37,38], vitreous hemorrhage may occur in some patients[22]. Some of these adverse events can be reduced with a dose of less than 50 micrograms[37]. To perform the subretinal injection of the tissue plasminogen activator, a 39-Gauge or thinner needle should be available. The subretinal injection is most commonly used with adjunctive intravitreal gas displacement or heavy liquids. Despite the great variability of reports, most patients (up to 80%) initially improve some degree of vision[23]. However, the longer duration of follow-ups, the more vision that declines; in addition, some reports even find no differences in the final vision whether or not the tissue plasminogen activator was used[17,39].

In relation to vitrectomy with subretinal clot removal, the Submacular Surgery Trial did not report differences in vision at two years compared to observation[17]. Reported complications, secondary to the surgical procedure, include vitreous hemorrhage (8 - 20%) [19,21,38], retinal detachment (up to 25%)[23,38,39], endophthalmitis (7%)[40] and epiretinal membrane (9%)[23]. In the Submacular Surgery Trial report, 16% of the operated eyes developed rhegmatogenous retinal detachment during the 12 months of follow-up, while only 2% in the observation group had it within 36 months of follow-up[41].

Photodynamic therapy with the use of verteporfin has been used in macular hemorrhages secondary to age-related macular degeneration, although with limited visual results[19,42]. Although its use has declined with the rise of anti-vascular endothelial growth factor drugs, its role, especially in polypoidal choroidal vasculopathy, is important[19].

Macular translocation consists of repositioning a functional area of the foveal neurosensory retina, originally located on the damaged retinal pigment epithelium, over a healthy area of this epithelium. It is an interesting therapeutic alternative with some reasonably positive results in submacular hemorrhages. Despite this, it should be reserved for patients with a very low initial visual acuity due to the complexity of the procedure and the high risk of significant vitre-

oretinal complications, such as epiretinal membranes, retinal detachment, vitreoretinal proliferation, recurrence of choroidal neovascularization or choroidal hemorrhage[19,43].

Conclusion

Proper and timely management of macular hemorrhages can achieve a good visual outcome, especially when its location is preretinal. Taking into consideration the risks and benefits from the procedures described, we consider that surgery to manage macular hemorrhage may not be considered as the first option. It is recommended to individualize each case to determine treatment, using the options described above.

Notes

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All authors contributed equally to conceptualization, methodology, formal analysis, investigation, and writing (review and editing), supervision, manuscript preparation and project administration.

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Ethics
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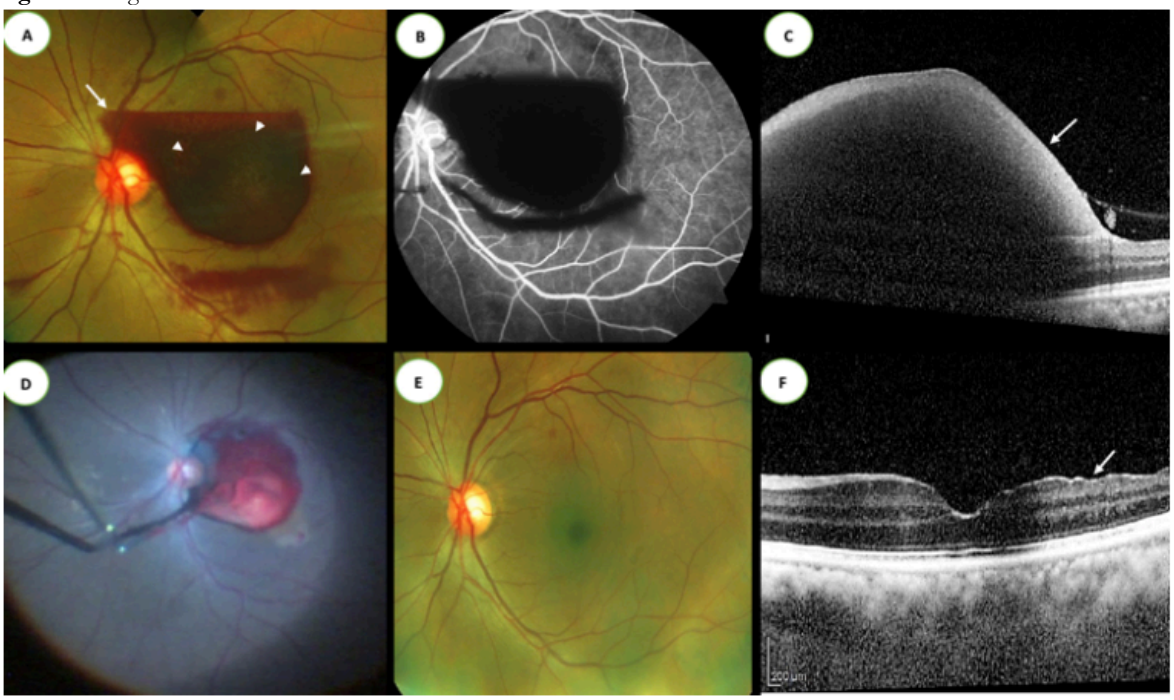
References

1. Bopp S, Mirshahi A. Management of Macular Hemorrhage. Springer. 2018. Classification of Macular Hemorrhages;11-21. | CrossRef |
2. Hochman MA, Seery CM, Zarbin MA. Pathophysiology and management of subretinal hemorrhage. Surv Ophthalmol. 1997 Nov-Dec;42(3):195-213. | CrossRef | PubMed |
3. Kunavisarut P, Thithuan T, Patikulsila D, Choovuthayakorn J, Watanachai N, Chaikitmongkol V, et al. Submacular Hemorrhage: Visual Outcomes and Prognostic Factors. Asia Pac J Ophthalmol (Phila). 2018 Mar-Apr;7(2):109-113. | CrossRef | PubMed |
4. Mizutani T, Yasukawa T, Ito Y, Takase A, Hirano Y, Yoshida M, et al. Pneumatic displacement of submacular hemorrhage with or without tissue plasminogen activator. Graefes Arch Clin Exp Ophthalmol. 2011 Aug;249(8):1153-7. | CrossRef | PubMed |
5. Auriol S, Mahieu L, Lequeux L, Quintyn JC, Pagot-Mathis V. [Pars plana vitrectomy, subretinal injection of recombinant tissue plasminogen activator and fluid-gas exchange in the management of massive submacular hemorrhages secondary to age-related macular degeneration]. J Fr Ophtalmol. 2010 Feb;33(2):84-91. | CrossRef | PubMed |
6. Lee JP, Park JS, Kwon OW, You YS, Kim SH. Management of Acute Submacular Hemorrhage with Intravitreal Injection of Tenecteplase, Anti-vascular Endothelial Growth Factor and Gas. Korean J Ophthalmol. 2016 Jun;30(3):192-7. | CrossRef | PubMed |
7. Johnson MW. Pneumatic displacement of submacular hemorrhage. Curr Opin Ophthalmol. 2000 Jun;11(3):201-6. | CrossRef | PubMed |
8. Durukan AH, Kerimoglu H, Erdurman C, Demirel A, Karagul S. Long-term results of Nd:YAG laser treatment for premacular subhyaloid haemorrhage owing to Valsalva retinopathy. Eye (Lond). 2008 Feb;22(2):214-8. | CrossRef | PubMed |
9. Li N, Zhu Z, Yi G, Li S, Han X. Valsalva Retinopathy in Twin-Pregnancy: A Case Report and Literature Review. Am J Case Rep. 2018 Jan 2;19:5-9. | CrossRef | PubMed |
10. Kuhn F, Morris R, Witherspoon CD, Mester V. Terson syndrome. Results of vitrectomy and the significance of vitreous hemorrhage in patients with subarachnoid hemorrhage. Ophthalmology. 1998 Mar;105(3):472-7. | CrossRef | PubMed |
11. De Maeyer K, Van Ginderdeuren R, Postelmans L, Stalmans P, Van Calster J. Sub-inner limiting membrane haemorrhage: causes and treatment with vitrectomy. Br J Ophthalmol. 2007 Jul;91(7):869-72. | CrossRef | PubMed |
12. García Fernández M, Navarro JC, Castaño CG. Long-term evolution of Valsalva retinopathy: a case series. J Med Case Rep. 2012 Oct 10;6:346. | CrossRef | PubMed |
13. Mennel S. Subhyaloidal and macular haemorrhage: localisation and treatment strategies. Br J Ophthalmol. 2007 Jul;91(7):850-2. | CrossRef | PubMed |
14. Aumiller MS, Rinehart J. Multi-layered haemorrhage secondary to retinal arterial macroaneurysm: a case report and review. Clin Exp Optom. 2015 Mar;98(2):117-21. | CrossRef | PubMed |
15. Goldenberg D, Soiberman U, Loewenstein A, Goldstein M. Heidelberg spectral-domain optical coherence tomographic findings in retinal artery macroaneurysm. Retina. 2012 May;32(5):990-5. | CrossRef | PubMed |
16. Toth CA, Morse LS, Hjelmeland LM, Landers MB 3rd. Fibrin directs early retinal damage after experimental subretinal hemorrhage. Arch Ophthalmol. 1991 May;109(5):723-9. | CrossRef | PubMed |
17. Hawkins BS, Bressler NM, Miskala PH, Bressler SB, Holekamp NM, Marsh MJ, et al. Surgery for subfoveal choroidal neovascularization in age-related macular degeneration: ophthalmic findings: SST report no. 11. Ophthalmology. 2004 Nov;111(11):1967-80. | CrossRef | PubMed |
18. Shin JY, Lee JM, Byeon SH. Anti-vascular endothelial growth factor with or without pneumatic displacement for submacular hemorrhage. Am J Ophthalmol. 2015 May;159(5):904-14.e1. | CrossRef | PubMed |
19. Stanescu-Segall D, Balta F, Jackson TL. Submacular hemorrhage in neovascular age-related macular degeneration: A synthesis of the literature. Surv Ophthalmol. 2016 Jan-Feb;61(1):18-32. | CrossRef | PubMed |
20. Varma R, Bressler NM, Doan QV, Gleeson M, Danese M, Bower JK, et al. Prevalence of and risk factors for diabetic macular edema in the United States. JAMA Ophthalmol. 2014 Nov;132(11):1334-40. | CrossRef | PubMed |
21. Olivier S, Chow DR, Packo KH, MacCumber MW, Awh CC. Subretinal recombinant tissue plasminogen activator injection and pneumatic displacement of thick submacular hemorrhage in Age-Related macular degeneration. Ophthalmology. 2004 Jun;111(6):1201-8. | CrossRef | PubMed |
22. Haupert CL, McCuen BW 2nd, Jaffe GJ, Steuer ER, Cox TA, Toth CA, et al. Pars plana vitrectomy, subretinal injection of tissue plasminogen activator, and fluid-gas exchange for displacement of thick submacular hemorrhage in age-related macular degeneration. Am J Ophthalmol. 2001 Feb;131(2):208-15. | CrossRef | PubMed |
23. Kamei M, Tano Y, Maeno T, Ikuno Y, Mitsuda H, Yuasa T. Surgical removal of submacular hemorrhage using tissue plasminogen activator and perfluorocarbon liquid. Am J Ophthalmol. 1996 Mar;121(3):267-75. | CrossRef | PubMed |
24. Thompson JT, Sjaarda RN. Vitrectomy for the treatment of submacular hemorrhages from macular degeneration: a comparison of submacular hemorrhage/membrane removal and submacular tissue plasminogen activator-assisted pneumatic displacement. Trans Am Ophthalmol Soc. 2005;103:98-107; discussion 107. | PubMed |

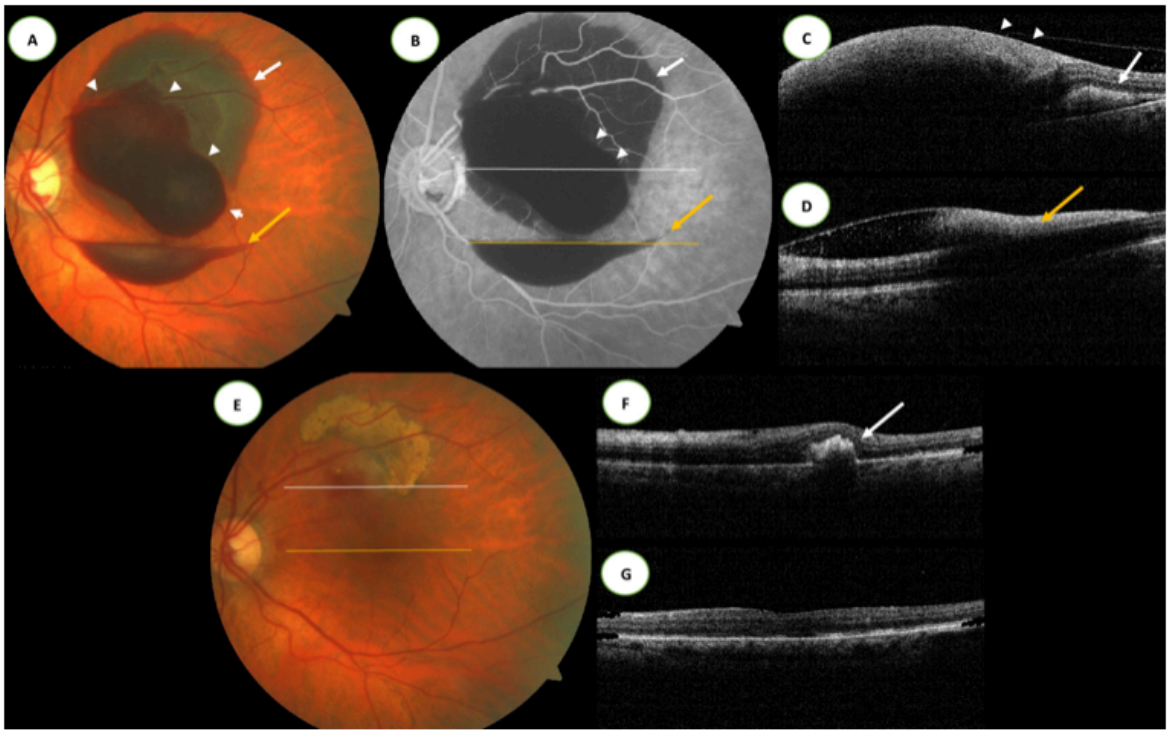
25. Scheider A, Gündisch O, Kampik A. Surgical extraction of subfoveal choroidal new vessels and submacular haemorrhage in age-related macular degeneration: results of a prospective study. Graefes Arch Clin Exp Ophthalmol. 1999 Jan;237(1):10-5. | CrossRef | PubMed |
26. Stifter E, Michels S, Prager F, Georgopoulos M, Polak K, Hirn C, et al. Intravitreal bevacizumab therapy for neovascular age-related macular degeneration with large submacular hemorrhage. Am J Ophthalmol. 2007 Dec;144(6):886-892. | CrossRef | PubMed |
27. Shienbaum G, Garcia Filho CA, Flynn HW Jr, Nunes RP, Smiddy WE, Rosenfeld PJ. Management of submacular hemorrhage secondary to neovascular age-related macular degeneration with anti-vascular endothelial growth factor monotherapy. Am J Ophthalmol. 2013 Jun;155(6):1009-13. | CrossRef | PubMed |
28. Mayer WJ, Hakim I, Haritoglou C, Gandorfer A, Ulbig M, Kampik A, et al. Efficacy and safety of recombinant tissue plasminogen activator and gas versus bevacizumab and gas for subretinal haemorrhage. Acta Ophthalmol. 2013 May;91(3):274-8. | CrossRef | PubMed |
29. Nourinia R, Bonyadi MH, Ahmadieh H. Intravitreal Expansile Gas and Bevacizumab Injection for Submacular Hemorrhage Due to Neovascular Age-related Macular Degeneration. J Ophthalmic Vis Res. 2010 Jul;5(3):168-74. | PubMed |
30. Arias L, Monés J. Transconjunctival sutureless vitrectomy with tissue plasminogen activator, gas and intravitreal bevacizumab in the management of predominantly hemorrhagic age-related macular degeneration. Clin Ophthalmol. 2010 Feb 18;4:67-72. | CrossRef | PubMed |
31. van Zeeburg EJ, van Meurs JC. Literature review of recombinant tissue plasminogen activator used for recent-onset submacular hemorrhage displacement in age-related macular degeneration. Ophthalmologica. 2013;229(1):1-14. | CrossRef | PubMed |
32. Chen YY, Lin LY, Chang PY, Chen FT, Mai ELC, Wang JK. Laser and Anti-Vascular Endothelial Growth Factor Agent Treatments for Retinal Arterial Macroaneurysm. Asia Pac J Ophthalmol (Phila). 2017 Sep-Oct;6(5):444-449. | CrossRef | PubMed |
33. Zweifel SA, Tönz MS, Pfenninger L, Becker M, Michels S. Intravitreal anti-VEGF therapy for retinal macroaneurysm. Klin Monbl Augenheilkd. 2013 Apr;230(4):392-5. | CrossRef | PubMed |
34. Tsakpinis D, Nasr MB, Tranos P, Krassas N, Giannopoulos T, Symeonidis C, et al. The use of bevacizumab in a multilevel retinal hemorrhage secondary to retinal macroaneurysm: a 39-month follow-up case report. Clin Ophthalmol. 2011;5:1475-7. | CrossRef | PubMed |
35. Cakir M, Cekiç O, Yilmaz OF. Pneumatic displacement of acute submacular hemorrhage with and without the use of tissue plasminogen activator. Eur J Ophthalmol. 2010 May-Jun;20(3):565-71. | PubMed |
36. Abdelkader E, Yip KP, Cornish KS. Pneumatic displacement of submacular haemorrhage. Saudi J Ophthalmol. 2016 Oct-Dec;30(4):221-226. | CrossRef | PubMed |
37. Chen SN, Yang TC, Ho CL, Kuo YH, Yip Y, Chao AN. Retinal toxicity of intravitreal tissue plasminogen activator: case report and literature review. Ophthalmology. 2003 Apr;110(4):704-8. | CrossRef | PubMed|
38. Hesse L, Schmidt J, Kroll P. Management of acute submacular hemorrhage using recombinant tissue plasminogen activator and gas. Graefes Arch Clin Exp Ophthalmol. 1999 Apr;237(4):273-7. | CrossRef| PubMed |
39. Ibanez HE, Williams DF, Thomas MA, Ruby AJ, Meredith TA, Boniuk I, et al. Surgical management of submacular hemorrhage. A series of 47 consecutive cases. Arch Ophthalmol. 1995 Jan;113(1):62-9. | CrossRef | PubMed |
40. Hassan AS, Johnson MW, Schneiderman TE, Regillo CD, Tornambe PE, Poliner LS, et al. Management of submacular hemorrhage with intravitreous tissue plasminogen activator injection and pneumatic displacement. Ophthalmology. 1999 Oct;106(10):1900-6; discussion 1906-7. | CrossRef | PubMed |
41. Bressler NM, Bressler SB, Childs AL, Haller JA, Hawkins BS, Lewis H, et al. Surgery for hemorrhagic choroidal neovascular lesions of age-related macular degeneration: ophthalmic findings: SST report no. 13. Ophthalmology. 2004 Nov;111(11):1993-2006. | CrossRef | PubMed |
42. Ahmad S, Bearelly S, Stinnett SS, Cooney MJ, Fekrat S. Photodynamic therapy for predominantly hemorrhagic lesions in neovascular age-related macular degeneration. Am J Ophthalmol. 2008 Jun;145(6):1052-1057. | CrossRef | PubMed |
43. Wong D, Stanga P, Briggs M, Lenfestey P, Lancaster E, Li KK,et al. Case selection in macular relocation surgery for age related macular degeneration. Br J Ophthalmol. 2004 Feb;88(2):186-90. | CrossRef | PubMed |

Figure 1. Images case 1.



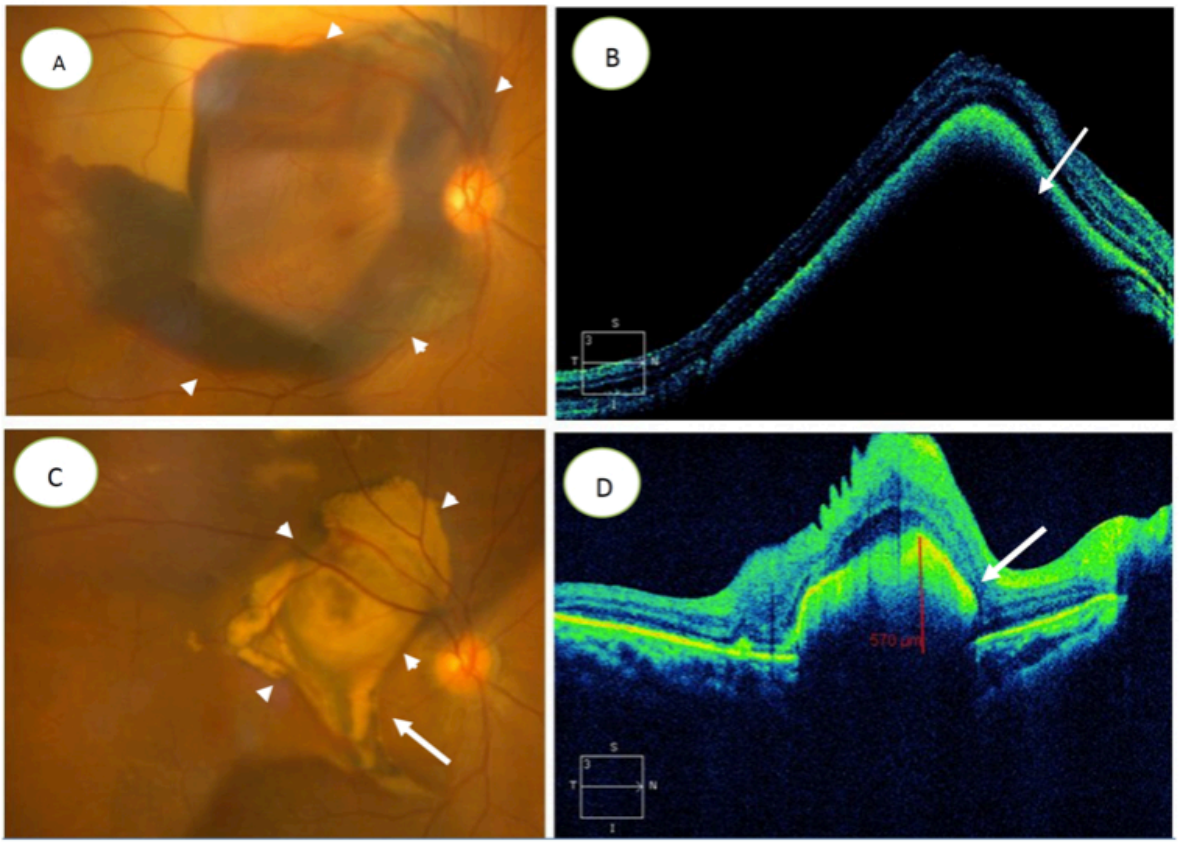
A: Fundus photography of a patient with Valsalva retinopathy: Note the extensive preretinal hemorrhage is observed in the posterior pole of the left eye covering most of the macula, including the fovea, with a level (white arrow) which suggests a subhyaloid hemorrhage; a slight glistening light reflex from the internal limiting membrane overlying the hemorrhage can be observed (white arrowhead) compatible with sub-internal limiting membrane hemorrhage.
B: Fluorescein angiography showing a large hypofluorescent lesion due to blockage, with no evidence of leakage.
C: Macular optical coherence tomography showing a dense (hyperreflective material) hemorrhage below the internal limiting membrane (*white arrow*)**.**
D: Release of the hemorrhage during 25-Gauge pars plana vitrectomy and internal limiting membrane peeling**.**
E: Fundus photography 4 weeks after the procedure, with no evidence of hemorrhage.
F: Optical coherence tomography: After 1 month, a temporal inner retinal defect is shown with small folds on its surface (*white arrow*).

Figure 2. Images case 2.



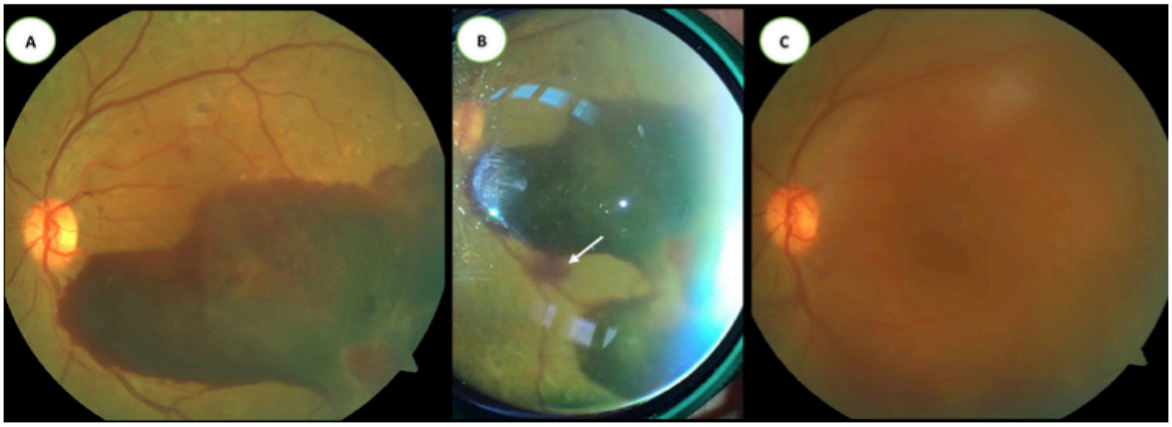
A: Fundus photography of a patient with an extensive multilevel retinal hemorrhage: The lesion covers most of the macula, including the fovea, due to a ruptured retinal arteriolar macroaneurysm. Note the subretinal component under the retinal vessels (*white arrow*), the sub-internal limiting membrane lesion with a glistening light reflex on the well-defined hemorrhage (*white arrowheads*) and the inferior boat-shaped subhyaloid hemorrhage (*yellow arrow*).
B: Fluorescein angiography demonstrating a large hypofluorescent lesion at various levels due to retinal (*white arrowheads* and *yellow arrow*) and choroid (*white arrow*) blockage without any leakage lesion.
C, D: Optical coherence tomography: Showing a dense hyperreflective lesion at various levels of the retina (subretinal -*white arrow*-, sub-internal limiting membrane -*white arrowheads*- and subhyaloid -*yellow arrow*-) that blocks the visualization of the underlying structures. **E:** Fundus photography: Eight weeks after pneumatic displacement, intravitreal ranibizumab and application of retinal laser photocoagulation in the causal lesion.
F, G: Optical coherence tomography: Two months later, an epiretinal membrane and a small subretinal fibrotic lesion near the superior arcade (*white arrow*) is shown.

Figure 3. Images case 3.



A: Fundus photography of a patient with a subretinal hemorrhage due to a choroidal rupture after an ocular trauma. Note the extensive subretinal hemorrhage that affects the entire posterior pole with foveal involvement extending beyond the temporal vascular arcades (*white arrowheads*).
B: Optical coherence tomography: Showing extensive submacular hemorrhage with posterior shadowing, obscuring the underlying structures. Note the marked retinal detachment and the hyperreflective material that represents the blood clot under the retina (*white arrow*).
C: Fundus photography: Two months after surgery, an extensive subretinal deposit of yellowish material is shown through the macula causing elevation, especially in the superior temporal vascular arcade (*white arrowheads*) and a choroidal rupture (*arrow white*).
D: Optical coherence tomography: Shows accumulation of subretinal hyperreflective material (570 micrometers high) with posterior attenuation, corresponding to fibrosis.

Figure 4. Images case 4.



A: Fundus photography of a patient with proliferative diabetic retinopathy demonstrating an extensive well demarcated pre retinal (sub-internal limiting membrane) hemorrhage involving the fovea (A glistening light reflex reflected from the internal limiting membrane overlying the hemorrhage can be observed) in the left eye.
B: The same patient immediately after hyaloidotomy/menbranotomy with neodymium-doped yttrium aluminium garnet laser. Note the drainage of premacular hemorrhage (*white arrow*).
C: Resolution of sub-internal limiting membrane hemorrhage after 2 weeks, associated with mild vitreous hemorrhage.

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