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Major review

Submacular hemorrhage in neovascular age-related macular degeneration: A synthesis of the literature

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ABSTRACT

Large submacular hemorrhage, an uncommon manifestation of neovascular age-related macular degeneration, may also occur with idiopathic polypoidal choroidal vasculopathy. Submacular hemorrhage damages photoreceptors owing to iron toxicity, fibrin meshwork contraction, and reduced nutrient flux, with subsequent macular scarring. Clinical and experimental studies support prompt treatment, as tissue damage can occur within 24 hours. Without treatment the natural history is poor, with a mean final visual acuity (VA) of 20/1600. Reported treatments include retinal pigment epithelial patch, macular translocation, pneumatic displacement, intravitreal or subretinal tissue plasminogen activator, intravitreal anti-vascular endothelial growth factor (VEGF) drugs, and combinations thereof. In the absence of comparative studies, we combined eligible studies to assess the VA change before and after each treatment option. The greatest improvement occurred after combined pars plana vitrectomy, subretinal tissue plasminogen activator, intravitreal gas, and anti-vascular endothelial growth factor treatment, with VA improving from 20/1000 to 20/400. The best final VA occurred using combined intravitreal tissue plasminogen activator, gas, and anti-vascular endothelial growth factor therapy, with VA improving from 20/200 to 20/100. Both treatments had an acceptable safety profile, but most studies were small, and larger randomized controlled trials are needed to determine both safety and efficacy.

1. Definitions

Submacular hemorrhage (SMH), an accumulation of blood between the neurosensory retina and the retinal pigment epithelium (RPE) arising from the choroidal or retinal circulation within the macular region, is a term most often used in the context of eyes with neovascular age-related macular degeneration (AMD). SMHs can also occur under the RPE. Lesions less than 1 disk diameter (DD) are often not labeled as SMH and are instead considered within the normal

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spectrum of neovascular AMD. Larger bleeds are often classified by their size, with a small SMH measuring at least 1 DD, but smaller than 4 DDs, a medium-sized SMH measuring at least 4 DD, but not extending beyond the temporal vascular arcade, and a massive SMHs extending beyond the temporal arcades.[35,117] SMHs are usually less than 500 microns thick, but they are sometimes labeled as thick SMHs if greater than 500 microns. Thick SMHs produce obvious elevation of the retina with obscuration of the RPE on fundus examination.[18]

2. Demographics

Retinal hemorrhage is a well-known feature of neovascular AMD, but large SMHs are thought to be much less frequent. In one study, 17% of patients with pigment epithelial detachment and AMD lesions developed SMH during the course of their disease, but large SMHs are likely to be much less common across the spectrum of AMD.[110] Anticoagulation,[74,83,141] and to a lesser extent antiplatelet[74,83] treatment, may increase the risk, particularly when combined with arterial hypertension.[30,83,86] Treatment of choroidal neovascularization (CNV) with both photodynamic therapy (PDT)[28,101] and anti-vascular endothelial growth factor (VEGF) agents have also been associated with SMH, with reports in patients receiving both ranibizumab and bevacizumab.[43,72,73,81] For example, Goverdhan and Lochhead reported that 40% of patients with large occult CNV developed SMH after treatment with bevacizumab.[43] The incidence of SMH may be higher among patients receiving a treat-as-needed anti-VEGF regimen, compared to a monthly anti-VEGF regimen.[84] Although many of these associations may be biologically plausible, particularly the association with anticoagulants and antiplatelet drugs, the data do not in themselves establish causation. Of note, most phase III trials of drugs or devices targeting AMD excluded patients with SMHs.

3. Clinical features

3.1. *Symptoms*

SMH causes progressive or sudden visual loss, according to the extent and thickness of the hemorrhage. This, and perhaps also fellow eye acuity, may partly explain the wide variability of when patients present, ranging from 24 hours to 10 months.[123] Mean initial visual acuity (VA) was 20/200, with 27% worse than 20/400.[123] A central scotoma was present in 90%, whereas 25% denied metamorphopsia, albeit in the context of severe visual loss.[123] In one consecutive series, 8 of 9 patients presented with SMH as the first manifestation of neovascular AMD.[106]

3.2. *Signs*

There is a distinction between subretinal hemorrhage and sub-RPE hemorrhage (Fig. 1). The first is located between the photoreceptor layers and the RPE. The hemorrhage is usually large, bright red, with relatively indistinct margins. In the second, the blood lies between the RPE and Bruch membrane. The blood has a dark-red, almost black appearance, and the margins

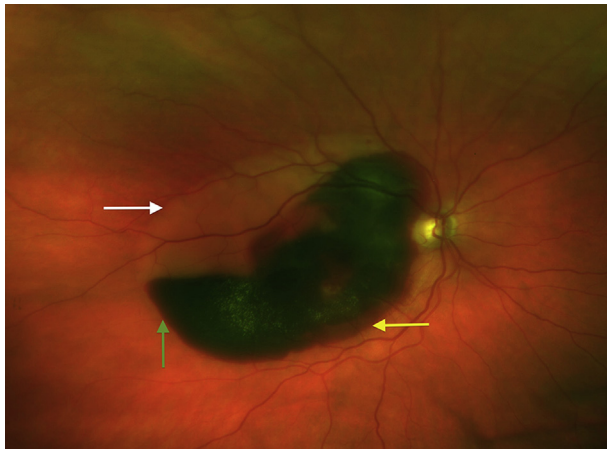

Fig. 1 – Fundus photograph of submacular hemorrhage. A thin layer of blood in the subretinal space (*horizontal yellow arrow*) has a light red appearance, and surrounds the inferior margin of a large pigment epithelial detachment that is partly filled with blood. The subretinal pigment epithelial blood appears much darker than the subretinal blood and has a discrete margin (*vertical green arrow*). The *white horizontal arrow* shows the superior margin of the pigment epithelial detachment, which is free of blood. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of the hemorrhages are well defined. Both may coexist. Typical features of neovascular AMD are usually present, such as drusen in the affected and fellow eye. There may also be features of idiopathic polypoidal choroidal vasculopathy (IPCV), which is responsible for about 20% of SMH in some series.[106]

4. Investigations

4.1. *Optical coherence tomography*

Optical coherence tomography helps localize the hemorrhage within the retinal layers and can objectively quantify SMH size. A typical SMH (Fig. 2) results in elevation of the overlying neurosensory retina, sometimes markedly so. The subretinal blood is defined on optical coherence tomography as a hyporeflective space of variable density, inducing a shadow effect. A sub-RPE (Fig. 2) hemorrhage lifts the RPE and appears as a hyporeflective band behind the RPE and is also associated with a shadow effect.

4.2. *Fluorescein angiography*

The subretinal and sub-RPE blood can produce so much masking that fluorescein angiography may offer limited information in the acute phase. Sometimes, CNV can be seen under a thin SMH or if they are located at the edge of the SMH.

4.3. *Indocyanine angiography*

Indocyanine green angiography may be more helpful than fluorescein angiography in helping to detect and localize CNV