Progressive Massive Choroidal Neovascularization, an Aggressive Phenotype: Case Report

Renata García-Franco\textsuperscript{a, b, c}, Marlon García-Roa\textsuperscript{a, b}, Roberto Cárdenas-Almagro\textsuperscript{d}, Diego Valera-Cornejo\textsuperscript{a, b}, Sergio E. Hernández-Da Mota\textsuperscript{e, f}

\textsuperscript{a}Retina Department, Instituto de La Retina Del Bajío, INDEREB, Santiago de Querétaro, Mexico; \textsuperscript{b}Retina Department, Instituto Mexicano de Oftalmología I.A.P, Santiago de Querétaro, Mexico; \textsuperscript{c}Posgraduate School, Universidad Nacional Autónoma de México, Ciudad de México, Mexico; \textsuperscript{d}Ocular Ultrasound Service, Clínica David, Unidad Oftalmológica, Morelia, Mexico; \textsuperscript{e}Retina Department, Clínica David, Unidad Oftalmológica, Morelia, Mexico; \textsuperscript{f}Retina Department, Clínica David, Unidad Oftalmológica, Morelia, Mexico; \textsuperscript{g}Postgraduate School, School of Medicine, Universidad Michoacana de San Nicolás de Hidalgo, Morelia, Mexico

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Abstract
We report 2 cases of an aggressive choroidal neovascularization phenotype. A 77-year-old hypertensive woman, with a 4-year history of visual loss in her left eye, due to vitreous hemorrhage associated with a dome-shaped mass lesion underwent pars plana vitrectomy. An extensive subretinal hemorrhage was found, associated with extensive subretinal fibrosis, which was treated with endophotocoagulation and intravitreal injection of anti-VEGF. Best-corrected visual acuity after surgery was light perception. A 74-year-old woman with a 4-year history of treatment for choroidal neovascularization in both eyes presented with an extensive subretinal hemorrhage associated with edema in the temporal peripheral retina. Lesions became larger despite monthly intravitreal anti-VEGF injections (14 injections) and verteporfin photodynamic therapy in both eyes. Throughout the years, the choroidal neovascular lesion continued to enlarge until it developed a severe vitreous hemorrhage. The patient rejected treatment and ended up with no light perception at the end of the follow-up (8 years). A rare severe choroidal neovascularization phenotype is presented here and would be considered to be at the aggressive extreme of the spectrum.
of a neovascular age-related macular degeneration or polypoidal choroidal vasculopathy that presents massive hemorrhage and exudation as much as in the posterior pole as in the peripheral retina.

Introduction

Choroidal neovascularization (CNV) is characterized by the growth of new blood vessels originating from the choroid that penetrate the Bruch membrane and reach the subretinal pigment epithelium (RPE) space. This process is the endpoint of various retinochoroidal entities, with age-related macular degeneration (AMD) being the most common cause [1]. Despite the fact that the neovascular form of AMD is present in only approximately 10% of patients, it is the most frequent cause of severe visual loss in people over 50 years of age [1]. These new blood vessels have an abnormal permeability that generates intraretinal and/or subretinal fluid, lipid deposits, and retinal hemorrhages that eventually generate a fibrotic lesion [2]. Usually, this disease is located in the macular region; however, a rare and aggressive neovascular phenotype has been described, characterized by massive choroidal neovascular membranes that extend beyond the equator, associated with extensive hemorrhages and serous retinal detachment [3, 4]. This aggressive phenotype has been described by Cheung et al. [3] as progressive massive CNV (PM-CNV). The clinical characteristics and course of PM-CNV patients are not well clarified. However, clinical findings are frequently bilateral and cause a profound loss of vision [3]. We present two cases with this particularly serious neovascular phenotype.

Cases

Case 1

A 77-year-old female patient presented with a history of unilateral visual loss in the last 4 years. The patient has a history of long-term systemic arterial hypertension (SAH) treated with amlodipine. Best-corrected visual acuity (BCVA) in her right eye (RE) was 20/50 and light perception in her left eye (LE). Intraocular pressure (IOP) was 16 mm Hg and 12 mm Hg in the RE and LE, respectively. The anterior segment examination did not show any alterations. Indirect ophthalmoscopy of the RE revealed multiple drusen in the posterior pole, while the LE revealed severe vitreous hemorrhage. B-scan ultrasonography showed the presence of a flat retinal detachment in the posterior pole, associated with extensive hemorrhages and serous retinal detachment of 3 disc diameters was observed (Fig. 1a). Endophotocoagulation surrounding the lesion with an intravitreal injection of 0.3 mg ranibizumab (Lucentis®; Novartis Pharma AG, Basel, Switzerland) and air tamponade was performed. Pictured here are the images of the fundus retinography (Fig. 1) and the optical coherence tomography (OCT) of the LE 2 weeks after the surgery. The OCT showed a dome-shaped lesion corresponding to an extensive retinal schisis, associated with an extensive subretinal fibrosis (Fig. 1d). Indocyanine green (ICG) angiography could not be performed. BCVA at the last visit (4 months) was light perception.
Case 2

A 74-year-old Hispanic woman without history of any systemic or ocular comorbidities presented bilateral visual loss over the course of 9 years. A family history of neovascular AMD was present in three of her siblings. We show the chronology of the lesions over time:

2010: BCVA was 20/40 in the RE and 20/100 in the LE. Under fundus examination, both eyes showed macular atrophic changes without foveal involvement, as well as the presence of extensive drusen in the posterior pole.

2012: Exudative lesions associated with visual loss began to appear in both eyes. An RPE detachment located temporal to the fovea was shown in the RE. In the LE, a large area of exudation that extended outside the superior temporal arcade was observed. The description of the fundus images are shown in Figure 2a, b. At that time, intravitreal anti-vascular endothelial growth factor (VEGF) therapy was started (monthly regime). During the course of that year, despite treatment, the RE developed a large disciform scar that extended beyond the vascular arcades (Fig. 2c, d).

2013–2014: In this period, both eyes presented three episodes of extensive and massive subretinal hemorrhage (Fig. 2e, f). In 2014, an ICG angiography was performed, showing...

**Fig. 1.** (a) Fundus photograph of the LE 2 weeks after surgery showing an extensive subretinal fibrosis in the posterior pole that extends outside the vascular arcades as well as multiple laser spots surrounding the lesion. (b) B-scan ultrasound of the left eye prior to surgery, showing a dome-shaped mass in the macular area associated with a flat retinal detachment and vitreous hemorrhage. (c) Fluorescein angiography of the left eye showing a large hyperfluorescent lesion due to retinal fibrosis and atrophy of the RPE. (d) OCT scan (paracentral to the fovea) showing an extensive retinal schisis, associated with subretinal fibrosis.
Fig. 2. (a) Fundus photograph of the RE in early 2012 showing exudation associated with atrophy in the macular area. (b) Fundus photograph from the LE at the beginning of 2012 showing a large area of exudation associated with subretinal hemorrhage around the superior temporal arcade. (c) Photographic composition of the RE fundus at 2013 showing a large subretinal hemorrhage over the peripapillary and macular area, as well as a large exudation in the temporal area of the macula. (d) Fundus photograph of the LE (2013) showing a large increase of the extensive subretinal hemorrhage and exudation. (e) Fundus photograph of the RE from 2014 showing an extensive subretinal fibrosis over the entire posterior pole associated with exudation and subretinal hemorrhage that extends outside the arcades. (f) Fundus photograph of the LE from 2014 showing great exudation associated with an extensive subretinal hemorrhage involving the macula. (g) ICG angiography showing the presence of multiple polyps in the temporal peripheral retina. (h) ICG angiography showing hyperfluorescence due to leakage in the temporal peripheral retina.
several clusters of nodular lesions (Fig. 2g, h) in the temporal retina compatible with polyps. Two sessions of photodynamic therapy (PDT) with verteporfin were applied in addition to intravitreal injections of 1.25 mg of bevacizumab (*Avastin; Roche, Basel, Switzerland*). Over the course of these years (2013–2014), the patient received a total of 14 intravitreal injections of bevacizumab on each eye.

2015: The patient developed a severe vitreous hemorrhage associated with a large-sized massive subretinal hemorrhage in the left eye, for which a B-scan ultrasound study was performed (Fig. 3a, b). Intravitreal injections continued in both eyes until the patient rejected treatment and did not attend follow-up visits for almost 4 years.

2019: At the last follow-up examination, both eyes presented BCVA of no light perception. Clinical examination revealed a flat anterior chamber, pupillary seclusion, rubeosis iridis, and an IOP of 34 mm Hg (Fig. 3c–e). In the B-scan ultrasound study, an extensive tractional retinal detachment was observed in both eyes (Fig. 3d, f).
Discussion

CNV is a process with a pathogenesis that implies both inflammation and angiogenesis, and its natural history involves three stages: proliferation of endothelial cells; migration of these cells through Bruch’s membrane; and formation of neovessels from these endothelial cells, developing a neovascular complex. For reasons not fully clarified, the neovascular complex undergoes an involutive process that manifests clinically with the appearance of a fibrotic lesion known as a disciform scar. Although disciform scars generally remain stable over time, they can present signs of activity, such as hemorrhage or exudation, suggesting that even chronic CNV can grow and cause greater deterioration of vision.

Recently, an aggressive neovascular AMD phenotype called PM-CNV has been described. PM-CNV lesions extend beyond the equator, are usually bilateral, and are associated with severe vision loss. Although it has rarely been described in the literature and its physiopathology is unknown, it has been observed that the extension of the lesion is produced as an aggressive reactivation on the borders of a disciform scar [3]. It would seem that in this phenotype, angiogenic activity predominates over fibrosis, which generates the extension of the hemorrhage from its borders; apparently, the coalescence of active or inactive lesions on its borders produces its extension towards the periphery. In addition to the hemorrhagic component, we also find serous and hemorrhagic detachments of the RPE, intra/subretinal fluid, retinal schisis, and extensive fibrosis that finally cause severe damage to the posterior pole and peripheral retina associated with significant deterioration of both central and peripheral vision. Cheung et al. [3] described a series of cases of 14 eyes (8 patients) with this phenotype variant during a median follow-up time of 10 years, reporting that the bilaterality of the cases corresponded to 75% (asymmetric presentation). The final BCVA in the majority of patients was hand movement, and 2 cases ended with the absence of light perception [3].

Vitreous hemorrhage as a complication of neovascular AMD is uncommon (2–6%) [2], and it has been reported that some patients (19%) with vitreous hemorrhage had a history of oral anticoagulant use (coumarin) [5]; however, Cheung et al. [3] reported that half of the patients in his study developed vitreous hemorrhage, and of these, more than half required pars plana vitrectomy.

In this aggressive phenotype, bilaterality, poor response to treatment, and severe loss of vision are common characteristics [3, 4]. Despite the fact that some cases were described before the era of anti-VEGF therapy (which could reflect the natural history of the disease), poor response to multiple treatments was frequent since neither anti-VEGF drugs, steroids, or PDT prevented the final outcome. Even when early treatment was started, constant reactivations over the years did not allow for an adequate treatment plan (case 1). Most of the patients at the last follow-up had BCVA of hand motion, but some patients ended up with no light perception (20–30%), which is unusual in neovascular AMD [2–4]. The absence of light perception in these patients could probably be explained by total retinal detachment, secondary glaucoma, or extensive peripapillary fibrosis that would generate an ischemic optic neuropathy (Case 2) [2].

Several therapeutic options have been described for the treatment of neovascular subretinal macular hemorrhages, such as intravitreal anti-VEGF drugs, pneumatic displacement with gas, laser therapy, and subretinal or intravitreal tissue plasminogen activator associated with vitrectomy. These therapeutic options have been used alone, in combination, and even sequentially. Despite treatment, patients with subretinal macular hemorrhage generally have a poor visual prognosis [6, 7]. Tissue plasminogen activator was not used in our cases due to its inaccessibility in our clinical setting.

Two entities that could be associated with the spectrum of this phenotype are polypoidal choroidal vasculopathy (PCV) and peripheral exudative hemorrhagic chorioretinopathy
(PECHR). PCV or aneurysmal type 1 neovascularization is considered to be a variant phenotype of neovascular AMD (despite presenting unique clinical manifestations) that sometimes presents with severe hemorrhagic and exudative lesions which can cause severe visual loss despite its usual favorable course [8]. PCV lesions tend to bleed easily (due to rupture of veins and occasionally arteries), producing extensive subretinal hemorrhages (30–63%) and even vitreous hemorrhage (4–19%) [8]. The risk of bleeding would increase over time (first year 2.4% and 29.8% at 10 years). It has been described that some morphological patterns (grape-like polyp clusters) would impose a significant risk factor for developing massive macular hemorrhage [9]. The activity of the clinical spectrum of PCV is variable, ranging from the presence of quiescent subclinical lesions to multiple lesions (grape-like polyp clusters) frequently associated with extensive hemorrhages. This aggressive PCV phenotype has been associated with a single nucleotide polymorphism in the genetic locus rs10490924 at LOC387715 (also known as age-related maculopathy susceptibility 2) and with the morphological pattern of “grape-like polyp clusters” [9, 10]. Usually, the presence of hemorrhages interferes with the performance of an ICG angiography to confirm the diagnosis; however, in one of our patients, we managed to carry out the study, revealing the typical lesions (case 2). The optimal treatment for PCV is still under debate and includes observation, PDT, anti-VEGF therapy, or combination therapy. PDT can cause hemorrhagic complications in 2.2–31% of treated eyes, which is seen in our second case; although the pathogeneses of these events are uncertain, it may be due to an excessive accumulation of blood through the rupture of fragile reperfused vessels or from a reactivation of VEGF after PDT.

On the other hand, it is believed that PECHR, a degenerative condition of the peripheral retina associated with hemorrhage and exudation, could be a peripheral variant of AMD or PCV (since it seems that they share a common neovascular component in their physiopathology). PECHR occasionally can cause extensive subretinal and/or vitreous hemorrhage [11]. Vascular changes similar to polyps have also been reported in the peripheral retina of patients with PECHR [12]. The clinical spectrum of PECHR may or may not be associated with the presence of polyps, and when the disease is associated with PCV, its course tends to resolve spontaneously with scar formation in most cases. However, less frequently, it can be more aggressive, producing massive subretinal and vitreous hemorrhage.

SAH has been reported to be associated with recurrent subretinal hemorrhage in patients with PCV. Polypoid vascular lesions are thought to be more likely to rupture and bleed causing subretinal hemorrhage when systemic blood pressure is high. PCV lesions have their own pulsation that would indicate their arterial component; therefore, they would have a higher intravascular pressure that would be transmitted from the internal choroidal vasculature, predisposing them to bleeding [13]. It is interesting to note that all patients reported by Cheung et al. [3] had SAH, although it is not possible to know whether systemic blood pressure was adequately controlled in their series. It would be possible that the unfavorable evolution of PM-CNV could be associated with arterial hypertension. In our case report, one of our patients had high blood pressure; however, we were unable to perform ICG angiography to rule out the presence of polyps as it was not available at the time.

This is a case report with several limitations due to its own nature; however, few cases have been reported describing this aggressive phenotype that we believe deserve awareness. PM-CNV is a rare phenotype that can be considered to be an aggressive form of the spectrum of a neovascular AMD, PCV, or PECHR that presents with manifestations as much as in the posterior pole as on the peripheral retina. It is characterized by lesions, often bilateral, that extend beyond the equator and have a poor visual prognosis. This phenotype is accompanied by episodes of reactivation that usually appear on the borders of disciform lesions, thus causing their large extension. Despite being chronic fibrotic lesions, they have the potential to grow and cause profound visual loss.
Statement of Ethics

This retrospective review of patients’ data did not require ethics approval according to local/national guidelines. Written informed consent was obtained from the patients for publication of this case report and any accompanying images. Any sort of information that might reveal the patient’s own identity has been completely avoided.

Conflict of Interest Statement

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Author Contributions

The authors confirm sole responsibility for the following: study conception, design, data collection, analysis and interpretation of results, and manuscript preparation. Renata García-Franco, Sergio E. Hernández-Da Mota, Roberto Cardenas-Almagro, and Marlon García-Roa were responsible for medical follow-up and treatment and have seen the patients at most intervals. Renata García-Franco and Sergio E. Hernández-Da Mota contributed to the design, data collection, analysis, interpretation of results, and manuscript preparation. Sergio E. Hernández-Da Mota, Renata García-Franco, and Diego Valera-Cornejo drafted the manuscript and created accompanying figures. Marlon García-Roa and Diego Valera-Cornejo contributed to data collection. Renata García-Franco, Sergio E. Hernández-Da Mota, Roberto Cardenas-Almagro, and Diego Valera-Cornejo provided critical revisions. All the authors approved the final version.

Data Availability Statement

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

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