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The long-term outcome of eyes with unexplained visual loss after gas tamponade for macula-on retinal detachment

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Short title: Vision loss after RRD: long-term

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Summary Statement

Eyes with macula-on rhegmatogenous retinal detachment suffering from unexplained visual loss after gas reabsorption disclose in the long-term an overall unchanged structural macular morphology and show a moderate, but significant, visual and perimetric improvement.

Keywords

Gas; Macula-on; Perimetric defect; Rhegmatogenous retinal detachment; Tamponade; Unexplained visual loss; Vitrectomy.

Abstract

Purpose: To analyze the long-term outcome of eyes suffering from unexplained visual loss after gas tamponade for primary macula-sparing rhegmatogenous retinal detachment (RRD).

Methods: Cross-sectional analysis of all eyes with macula-on RRD experiencing an unexplained loss of vision after gas reabsorption that were treated and followed from 2010 to 2019. The investigational work-up included: best-corrected visual acuity (BCVA), clinical examination, spectral-domain optical coherence tomography (SD-OCT) and automated computerized perimetry.

Results: The 9 eyes of the 9 patients were analyzed after 5.9±2.4 years. BCVA improved by 0.54±0.50 logMAR from baseline, achieving a final value of 1.17±0.52 logMAR (~20/320; *p*=0.0115). The thicknesses of the macula, of the macular ganglion cells and of the retinal nerve fiber layers were unchanged compared to the baseline, as well as the rate of ellipsoid zone defects (22.2%). The proportion of eyes with microcystoid macular edema (MME) significantly decreased to 44.4% (*p*=0.0294). Perimetry mean deviation increased from a baseline value of -18.06±2.72 to -17.23±2.29 dB (*p*=0.0390), with an unchanged pattern standard deviation (*p*=0.1289). In general, a reduction of the scotomata relative depth from baseline was evident in all eyes.

Conclusions: Eyes with macula-on RRD suffering from unexplained visual loss after gas reabsorption, despite disclosing an overall unchanged structural macular morphology, showed a moderate, but significant, visual and perimetric improvement in the long-term.

Introduction

Profound unexplained vision reduction is a rare and severe complication that may unexpectedly present after vitrectomy with gas tamponade for the treatment of primary macula-on rhegmatogenous retinal detachment (RRD). It is reported to occur with an incidence of 2.52/1000 eyes per year, and remains a serious concern for vitreoretinal surgeons.[1]

Despite a definite and unique pathological mechanism has not been described yet, the structural (optical coherence tomography [OCT]) and functional (computerized perimetry) imaging findings are consistent with a possible damage location within the retinal axonal structure.[1]

The present series aims to give further light to this unexpected and unpredictable complication, analyzing the long-term outcome of those eyes experiencing an unexplained loss of vision after gas reabsorption that were published in 2021.[1]

Brief Report

Ethics

All the procedures performed involving human participants were in accordance with the ethical standards of the Institutional Review Board of the San Raffaele Scientific Institute and with the 1964 Helsinki declaration and its later amendments. All patients signed a general informed consent form, which was specifically designed and approved by the Institutional Review Board of the San Raffaele Scientific Institute solely for participants of purely observational retrospective or cross-sectional studies.

Study protocol

In this cross-sectional observational series, we reanalyzed the 9 eyes of the 9 patients affected by macula-on primary RRD, treated in our center with vitrectomy and gas tamponade, that experienced a profound and unexplained visual loss after gas reabsorption. The institutional patients were operated by the same surgeon (MC) at the Vitreoretinal Surgery Division of the San Raffaele Scientific Institute in Milan from January 2010 to December 2019, and pertinent data were previously published.[1]

Patients were contacted and visited in our center, and underwent a general ophthalmological evaluation including structural spectral-domain OCT (SD-OCT) and automated computerized perimetry.

Investigated variables

The general ophthalmological evaluation included: ocular medical history & medications, best-corrected visual acuity (BCVA), complete eye examination, intraocular pressure (IOP), macular and optic nerve SD-OCT, automated computerized perimetry.

Distance BCVA was measured in dedicated offices with continuously monitored luminance, using the Early Treatment in Diabetic Retinopathy Study charts. The notation was converted into logMAR for ease of calculations.

SD-OCT images were performed using the Spectralis OCT device (Heidelberg Engineering, Heidelberg, Germany). Scans were evaluated for: central macular thickness (CMT), normal foveal contour (graded as present/absent), microcystoid macular edema (MME, graded as present/absent), ellipsoid zone (EZ) regularity (graded as regular/irregular), thickness of macular ganglion cells and circumferential optic nerve retinal nerve fiber layers (RNFL). For the sake of homogeneity with the previously gathered data, we considered the stacked thickness of the ganglion cell layer and the inner plexiform layer (GCL+IPL), averaging the values superior and inferior to the macular median raphe.

Computerized automated perimetries were conducted with a Humphrey visual field analyzer (Zeiss, Oberkochen, Germany) using a 30-2 pattern and under standard luminance and threshold parameters.

All the obtained measurements were compared with those acquired at the time of vision loss occurrence (referred as “baseline”), that were previously published.[1]

Statistical analysis

Data are reported as average values ± standard deviation. Statistical analyses were performed using Past 4.0 (Palaeontologica Electronica). The Fisher’s exact test was used to compare non-continuous variables while the Wilcoxon test was applied to compare the quantitative

measures. In all analyses, the Bonferroni correction was adopted for *p* values, and only <0.05 were considered significant.

Results

All the 9 patients completed the planned examinations. The average follow-up was 5.9±2.4 years (2.6-8.9, median 6.7). General medical conditions remained overall stable in all subjects: all maintained good health conditions, with only 1 patient with a previously known history of type-2 diabetes mellitus without retinopathy. None of them required any specific general or ocular medications, including IOP-lowering agents. All subjects were empirically suggested to take a 6-month course of an oral combination Q10 coenzyme and citicoline, which they all reported to have followed for 9.2±2.5 months.

All eyes were pseudophakic at the time of re-examination, as 5 of the 9 eyes that were phakic at the time of vision loss later underwent uneventful cataract extraction. Eye examination was in all cases unremarkable; IOP was 12.9±1.9 mmHg.

Visual acuity significantly improved by 0.54±0.50 logMAR (median 0.40) from baseline, achieving a final value of 1.17±0.52 logMAR (~20/320; p=0.0115) (Table 1). Only 1 eye disclosed a considerable vision improvement, with a final BCVA of 0.1 logMAR (starting from 1.9 logMAR).

The SD-OCT outcome measurements are depicted in the Table 1. The thicknesses of the central macula (CMT), of the macular ganglion cells (both superior and inferior) and of the RNFL (all quadrants) were unchanged compared to the baseline. The rate of ellipsoid zone defects (22.2%) was also unchanged. The foveal contour remained also regular in all (100%) the 9 eyes. The proportion of eyes with microcystoid macular edema (MME) significantly decreased to 44.4% (p=0.0294) (Figure 1).

All the 9 subjects repeated computerized perimetry. Average mean deviation (MD) increased, from a baseline value of -18.06±2.72 dB (median -18.83) to -17.23±2.29 dB (median -17.32, p=0.0390). Pattern standard deviation (PSD) remained unchanged, from 12.92±2.38 dB (median -13.74) of baseline to 12.67±2.44 dB (median -13.13, p=0.1289). All cases disclosed variable patterns, overall ascribable to a large central scotoma with a diffuse and nonspecific reduced retinal sensitivity, variably associated with peripheral defects. In general, a reduction of the scotomata relative depth from baseline was evident in all eyes (Figure 2). These findings agreed with the patient's subjective perception, that was reported as a gradual fading out of the blurred areas. Arcuate scotoma, that were not evident at baseline, never developed. Fellow eye perimetries kept all normal.

Discussion

The chance of losing vision after uncomplicated primary vitrectomy with gas to treat macula-on RRD is puzzling. Both the patient and the surgeon live with frustration this tragic event, as the first, who is usually retaining a very high visual capacity before surgery, is going to blame the second for the permanent disability.

Unexpected visual loss after macula-on RRD has been reported to occur much frequently with the use of silicone oil, from 20 to 33% of surgeries.[2] Numerous researchers aimed to provide answers to the unexplained nature of this problem, considering some hypothesis such as the dissolution of macular pigments in silicone oil, electrolyte imbalance, impaired perfusion and mechanical damage to nerve fibers.[3,4]

In cases treated with gas, the odds of this complication are very low, roughly 2.5 every 1000 surgeries per year. This phenomenon was extensively described in our recent work[1], where we argued about its pathological mechanisms and predicting factors. Briefly, the structural and functional imaging was found to be consistent with a possible damage location within the

retinal axonal structure, corroborated by the subnormal macular GCL and RNFL alterations and with the presence of MME. Our studies were though unable to identify any specific predicting or causative factor, actually leaving this chance as unexpected.

Despite this information might be considered useful for an appropriate surgeon-patient relationship, the prognosis of these eyes still remains unclear. We hence took advantage of our series to observe the long-term outcome (~6 years after vision loss) of these eyes and fill this knowledge void.

Even though the average final BCVA remained in a low range (<20/200), we found a significant visual increase in the long term. This visual improvement was also subjectively reported by the patients, who described a mild “thinning out” or “fading out” of the blurred areas in the visual field. Furthermore, these subjective impressions were documented by our perimetric findings, that show persistent scotomatous area but with a slight reduction in their relative depth (Figure 2). The quantitative perimetric parameters were indeed consistent with our findings: the MD, representing the average general sensitivity, turned out to be increased in contrast with an unchanged PSD, in turn representing the focal perimetric alterations.

Structural SD-OCT findings were, in contrast, overall stable. The macular thickness, as well as the thickness of the macular ganglion cell and the RNFL indeed remained similarly distributed compared to the baseline. The foveal architecture (OCT contour, EZ regularity) also kept equal. We though appreciated a halving of the MME rate (Figure 1). The MME, that is not to be related with retinal vascular impairment, is suggested to be caused by trans-synaptic retrograde degeneration of the inner retinal layers, resulting in impaired fluid reabsorption in the macula.[5]

These abovementioned features, a mild functional improvement associated with an overall anatomical stability, may at first appear inconsistent. We though speculate that, being the pathogenic trigger unique and not chronically distributed through time, the retinal structural

damage might have been severe but limited and resolved to the perioperative time. Once this retinal axonal impairment had occurred, possible compensative mechanisms may have begun, such as neuroadaptation or local homeostatic plasticity. These cellular pathways are called on in conditions such as glaucoma[6,7] or after multifocal IOL implantation[8], and imply the cellular neural network rearrangement. These adaptative phenomena are indeed consistent with our findings and insights, of an almost unchanged macular structure but associated with a subjective and objective improvement.

Whether the triggering event should be related to the time of surgery (pressurized air during fluid exchanges, mechanical damage by suction forces during posterior vitreous detachment induction) or to the immediate postoperative period (IOP elevation), this remains purely speculative. Given the clinical characteristics and the physiopathological insights that may be deducted from our investigation, we feel to recommend than any possible pressure-related damage, either intraoperative or postoperative, should be avoided. Keynotes of this control may rely on a rigorous intraoperative pressure monitoring, aided by valved trocars, and on smooth fluid-air exchanges, avoiding any air jet-related turbulence. The latter was indeed reported to be a possible causative factor of direct retinal damage in macular surgery.[9]

We are not in the position to state any therapeutic conclusion regarding our series, since any specific protocol neither a control group was designed. Subjects received an oral integration of Q10 coenzyme and citicoline combination for ~9 months, essentially based on the rationale of supporting the putative neuronal impairment.[10] Any clinical deduction should hence be taken cautiously.

We disclose the present investigation has significant limitations, at first intrinsically related to the very reduced numerosity. The statistical inferences should be therefore handled gingerly. This study also lacks a longitudinal observation, hence no temporal pathological assumption can be argued.

Despite mainly speculative, we however believe the observations made on our series can give further light to this unexpected occurrence and provide surgeons with useful clinical information regarding the prognosis. Future research, possibly supported by electrophysiological analyses or by microperimetry, may further expand the pathological bases of this feared complication.

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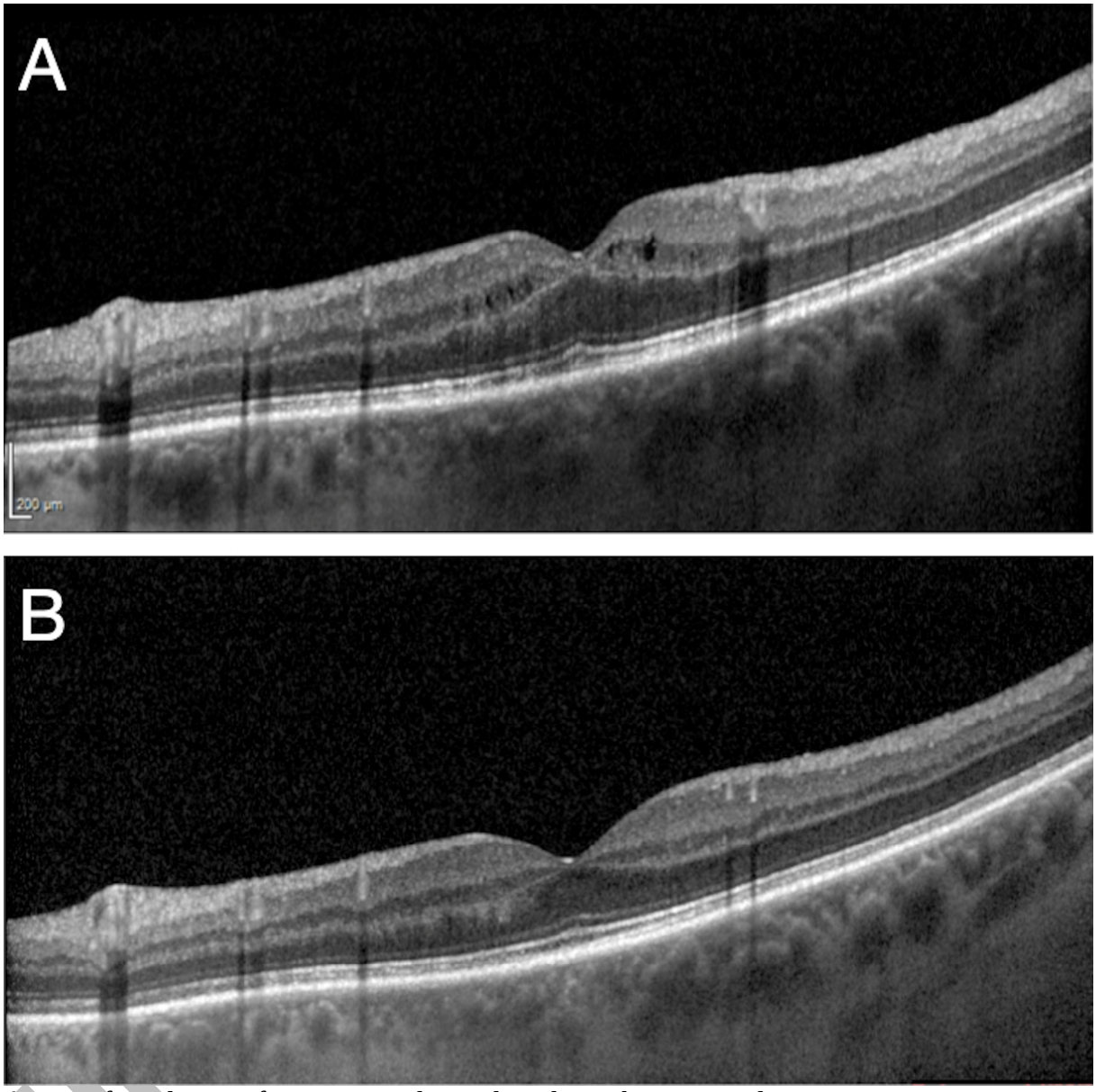
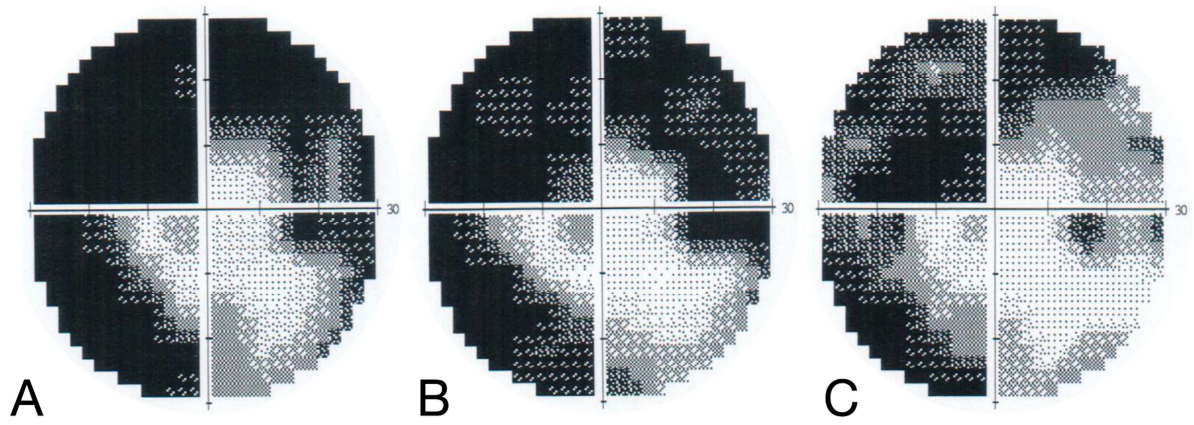
Figure legends

Figure 1. Resolution of microcystoid macular edema.



A case of resolution of microcystoid macular edema that occurred in an eye experiencing unexplained visual loss after gas tamponade for macula-on primary rhegmatogenous retinal detachment. The microcysts, predominantly evident in the inner plexiform layer, disappeared at the last follow-up (5 years after presentation).

Figure 2. Evolution of the visual field defects.



Visual field defects of the right eye of a patient affected by macula-on primary rhegmatogenous retinal detachment experiencing visual loss soon after gas reabsorption (A). 30-2 computerized automated perimetry shows a superior-nasal complete and absolute defect respecting the horizontal raphe and the vertical meridian, a blind spot enlargement, and two mid-peripheral (beyond 15° from fixation) absolute scotomata. Six months (B) and 53 months (more the 4 years) (C) after visual loss, the same pattern distribution of the scotomata is visible, with a progressive reduction in their relative depth.

Table 1.

Clinical characteristics of the 9 eyes of the 9 patients experiencing unexplained and profound vision loss after gas tamponade for macula-on primary rhegmatogenous retinal detachment. The newly acquired measurements are reported as “last follow-up”, and were compared with those taken at the time of vision loss occurrence (“Baseline”).

Data are shown as average values ± standard deviation (median).

		Baseline	**Last follow up**	***p***
Best corrected visual acuity (LogMAR)		1.72±0.28 (1.9)	1.17±0.52 (1.3)	**0.0115**
Central foveal thickness (µm)		241±12 (240)	243±10 (242)	0.2608
Microcystoid macular edema		9/9 (100%)	4/9 (44.4 %)	**0.0294**
Ellipsoid zone defect		2/9 (22.2%)	2/9 (22.2%)	1.0000
Macular ganglion cell thickness (µm)	Superior	60±10 (56)	60±9 (55)	0.8907
	Inferior	60±10 (55)	60±10 (56)	1.0000
Retinal nerve fiber layer thickness (µm)	Inferior	108±12 (102)	108±11 (103)	1.0000
	Superior	99±10 (96)	98±10 (97)	0.7257
	Nasal	83±13 (89)	82±14 (89)	0.1407
	Temporal	67±11 (66)	67±11(67)	0.4795