Bilateral angle-closure during hospitalization for coronavirus disease-19 (COVID-19): A case report

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Abstract

Purpose: This report describes a case of bilateral primary angle closure (PAC) progressing to unilateral end-stage primary angle closure glaucoma (PACG) associated with treatment for coronavirus disease-19 (COVID-19) infection.

Methods: A 64-year-old man came to our attention because of blurred vision after a 2-month hospital stay for treatment of COVID-19 infection. Examination findings revealed PACG, with severe visual impairment in the right eye and PAC in the left eye due to plateau iris syndrome. The patient’s severe clinical condition and prolonged systemic therapy masked the symptoms and delayed the diagnosis. Medical chart review disclosed the multifactorial causes of the visual impairment. Ultrasound biomicroscopy (UBM) aided in diagnosis and subsequent therapy.

Results: The cause behind the primary angle closure and the iridotrabecular contact was eliminated by bilateral cataract extraction, goniosynechialysis, and myotic therapy.

Conclusions: COVID-19 treatment may pose an increased risk for PAC. Accurate recording of patient and family ophthalmic history is essential to prevent its onset. Recognition of early signs of PAC is key to averting its progression to PACG.

Keywords
Angle closure, GLAUCOMA, diagnostic techniques, glaucoma medical therapies, anesthesia/sedation

Introduction

The Association of International Glaucoma Societies consensus classifies angle closure glaucoma (ACG) by its underlying mechanisms of onset: (1) pupillary block type; (2) plateau iris type; (3) lens factors (lens-induced glaucoma); and (4) malignant (ciliary block) glaucoma. Primary angle closure (PAC) and primary angle closure glaucoma (PACG) differ from secondary forms by the absence of a pre-existing eye condition that causes the anterior chamber angle to close (e.g. lens dislocation, prolonged inflammation, protruding vitreous, etc.) and arises from different conditions: pupillary block, plateau iris configuration, thick peripheral iris roll and exaggerated lens vault.

PACG could manifest clinically with increased intraocular pressure (IOP) in presence of glaucomatous optic neuropathy. Two forms are distinguished, acute and chronic PACG, and are often associated with subacute or intermittent angle closure to indicate self-limiting or remitting symptoms.

Chronic, intermittent, and acute forms may coexist: the chronic form may develop with gradual progressive closure of the angle or after acute primary angle closure (APAC). A nonlinear relationship exists between IOP and degree of peripheral anterior synechiae. Chronic PACG progresses in a gradual closure of the iridocorneal angle and results in blockage of the trabecular meshwork. Contact between the
irris root and the peripheral cornea in the pupillary block and in the plateau iris configuration consequent to the concurrent mixed effect of changes in anatomy (hyperopia, shorter axial length, thicker lens, shallow anterior chamber) can result from accommodation, pupil dilation, emotional stress, and body position.5–8

Patients hospitalized in an intensive care unit (ICU) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection are often positioned facedown (prone) to improve the ventilation/perfusion ratio and boost blood oxygen levels. The prone position is a known cause of increased IOP secondary to obstruction of the trabecular meshwork by the iris, which is pushed forward by hydrostatic and tissue pressure.9–11 Another cause of elevated IOP is the use of sympathomimetics in the ICU.12 These are known risk factors for PACG. The American Academy of Ophthalmology and a recent report by Bertoli et al. have warned about this potential risk; to our knowledge no cases during the present corona virus disease 2019 (COVID-19) pandemic have been reported.13,14

For this case report, all medical and surgical procedures were conducted in compliance with the tenets of the Declaration of Helsinki. Written, informed consent for the research use of clinical records and data was obtained from the patient. In brief, his medical chart was reviewed when he presented to the Ophthalmology Unit (University Eye Clinic of Verona) for a scheduled visit a few days after discharge because of reduced vision in both eyes he had noticed toward the end of his stay in the Pneumology Unit for respiratory rehabilitation. His ophthalmologic history was unremarkable. On routine eye exam by his ophthalmologist 3 months earlier, Snellen visual acuity was 20/20, with mild simple myopic with the rule astigmatism (~0.75 D in both eyes), normal anterior segment and posterior pole, and intraocular pressure (IOP, 12 mmHg) in both eyes. No measurements were recorded for anterior chamber depth or gonioscopy or visual field test or ocular coherence tomography (OCT) of the macular region, optic nerve, and ganglion cell.

**Materials and methods**

**Patient history, diagnosis, initial treatment**

A 64-year-old man in otherwise good health was admitted to the Infectious Disease Unit for treatment of COVID-19 infection after testing positive by a molecular test (PCR assay) performed the day before by his general practitioner. On admission, he had a history of 10 days of fever, cough, and progressive dyspnea. While in the Pneumology Unit, he breathed with the aid of an oxygen mask and received enoxeparin sodium 4000 IU (40 mg) per day, hydroxychloroquine 200 mg per day, and intravenous (IV) ceftriaxone 2 g per day. Two days later he was transferred to the Intensive Care Unit (ICU) due to rapid worsening in general condition: tachycardia, hypotension, hypercapnia, metabolic acidosis, and arterial blood O₂ pressure (pO₂, 50 mmHg) despite assisted breathing. He was promptly sedated, anesthetized, and intubated.

Sedation was obtained and maintained with remifentanil IV (5 mg/50 mL; 4 mL/h) and propofol 2% (20 mg/mL; 12 mL/h); roncuronium bromide (10 mg/mL; 5 mL/h) was administered for myorelaxation. Norepinephrine (8 mg/50 mL; 10 mL/h) was administered daily starting from the day of intubation for 37 consecutive days to manage systemic hypotonia. Morphone IV in a bolus of 2 mg (10 mg/ml) was given every 24 h throughout intubation. The patient remained intubated for 3 days during which he received five cycles of pronation, each lasting a mean of 9 h (range, 8.5–10.5 h, except for the third and longest which lasted 15 h).

After extubation, he remained sedated (propofol and dexomedine hydrochloride) for the next 34 days in the ICU. Two days after extubation, anisocoric pupils were noted: the pupil of the right eye was mydriatic and unresponsive to light, whereas the left eye was responsive to light (right and left pupillary diameter 6:3 mm). Cranial computed tomography (CT) to further investigate this finding was unremarkable. Ophthalmologic consultation was not sought at this point. Seven days later, anisocoric, unresponsive pupils were recorded on the patient’s chart (right and left pupillary diameter 6:3 mm).

The total ICU stay was 46 days (3 intubated, 34 sedated, 9 conscious), during which three episodes of atrial fibrillation were successfully medically cardioverted, and hydro pneumothorax and pericardiac effusion were uneventfully drained. He was then transferred to the Pneumology Unit for 3 weeks of respiratory rehabilitation, during which he was conscious and started to notice blurred vision and difficulties in focusing but without pain. He began to seriously worry about his impaired vision when he struggled to sign the hospital discharge form.

Five days later he came to our unit because of vision loss. Visual acuity was hand motion (HM) in the right eye and 20/25 Snellen in the left eye; anterior eye segment examination revealed no signs of conjunctival vessel dilation in either eye, clear cornea, shallow anterior chamber, a peripheral closed angle (Van Herick grade 0); both pupils were unresponsive to light, with mild mydriasis (right and left pupillary diameter 5:5 mm), there was diffuse iris atrophy, and localized depigmentation between the pupillary ruff and the collarate, cortical, and nuclear cataract (NO3, NC3 according to the Lens Opacities Classification System III (LOCS III) (Figure 1).15 IOP was 43 mmHg in the right eye and 24 mmHg in the left eye recorded using a Goldmann applanation tonometer (AT 900®, Haag-Streit International AG, Koeniz, Switzerland). Fundoscopy performed using a double aspheric 78 D lens revealed a pale, medium-sized optic disc with a cup-to-disc ratio of 0.9 in the right eye and 0.4 in the left eye; the macular region was normal.
OCT (Spectralis® OCT, Heidelberg Engineering, Heidelberg, Germany) of the optic nerve showed severe reduction of the fiber layer in 5 out of 6 quadrants in both minimum rim width (MRW) and retinal neural fiber layer thickness (RNFLT) in the right eye, whereas in the left eye the MRW was within the normal limits (albeit slightly reduced compared to database mean) and one borderline sector out of five normal sectors for the RNFLT (Figure 2). Ganglion cell layer (GCL) measurement revealed diffuse reduction in GCL volume and thickness in the right eye, while GCL volume and thickness were within the normal limits in all quadrants in the left eye (Figure 3). The macular region was normal in both eyes.

A visual field test was performed using the SITA Standard 24-2 program on a Humphrey® Field Analyzer 3 (Carl Zeiss Meditec, Dublin, CA, USA) (Figure 4). Dynamic contact gonioscopy with a Zeiss goniolens showed bilateral closure of the anterior chamber angle on 360° (Shaffer gonioscopy grading system 0; Spaeth gonioscopy grading system A 0° s-plateau configuration); the indentation maneuver (Forbes’ maneuver) did not enhance visualization of the trabecular meshwork. Finally, the angle and the ciliary process were investigated by sonographic analysis of the anterior segment using ultrasound biomicroscopy (UBM) with a 50 MHz transducer (Aviso™, Quantel Medical, Clermont-Ferrand, France). UBM performed with sonographic transverse scans oriented to the temporal meridian of the globe (OD 9 o’clock, OS 3 o’clock) showed complete anatomic obliteration of the trabeculum by the base of the iris in both eyes. Angle

**Figure 1.** Anterior segment of OD. Shallow anterior chamber, iris atrophy, and nuclear cataract.

**Figure 2.** OCT of minimum rim width (MRW) and retinal nerve fiber layer thickness (RNFLT): diffuse, advanced defect of the neural fibers in OD (Panel A), MRW within normal limits in all sectors, one borderline sector in the RNFLT in OS (Panel B).
Figure 3. OCT of the ganglion cell layer (GCL) showing a general reduction in volume and thickness in OD (Panel A) and volume and thickness within normal limits in OS (Panel B).

Figure 4. Visual field examination using the 24-2 SITA standard program on the Humphrey® Field Analyzer 3: (a) the numerical dB threshold values display a general absolute scotoma with a few locations and scotomatous points in OD, where extremely low light sensitivity still seems present (left panel), the visual field defect on the gray scale (right panel) and (b) normal light sensitivity in the numerical dB threshold values and on the gray scale in OS.
Closure due to plateau iris syndrome was diagnosed based on the findings of straight iris conformation and non-visualization of the sulcus ciliaris (Figure 5).

Axial eye length measurements (A-scan biometry) were taken with a 10 MHz focused transducer (Aviso™, Quantel Medical). The measurements confirmed the presence of a shallow anterior chamber as the biometric predisposing factor to angle closure (OD 1.68 mm, OS 1.76 mm), whereas axial length (OD 23.5 mm, OS 23.6 mm) and lens thickness (OD 3.76 mm, OS 4.03 mm) were within normal limits. Central endothelial cell density was measured with a single scan endothelial microscope (Perseus®, CSO, Florence, Italy) (OD 2078 cells/mm², OS 2356 cells/mm²).

Given the clinical, anatomical, and functional aspects, a similar surgical approach for both eyes was considered the best treatment option. Phacoemulsification with IOL in the bag implantation and goniosynechialysis were planned for deepening the anterior chamber and the iridocorneal angle and to prevent worsening of the left eye. Surgery on the right eye was performed the day after diagnosis, and then 7 days later on the left eye. Until the day of the surgery, pilocarpine 2% twice daily and a fixed combination of timolol 0.5% and brinzolamide 1% twice daily were administered to the left eye.

**Surgery**

A single rapid (<20 min) IV infusion of mannitol in 20% solution ended 30 min before the first operation (OD only). Standard cataract surgery was performed through a 2.2 mm corneal tunnel incision, followed by a phaco-chop technique using the Stellaris™ phaco-platform (Bausch & Lomb Inc, Rochester, NY, USA) and capsular bag intraocular lens (IOL) insertion. A dispersive/cohesive viscoelastic (2.3% sodium hyaluronate) solution was employed during phacoemulsification to protect the corneal endothelium. After IOL placement, the viscoelastic material was accurately removed from the anterior chamber with an irrigation/aspiration probe. An acetylcholine chloride 1% solution was injected intracameral to induce miosis. The angle was opened by infusion of a viscoelastic solution (1.4% sodium hyaluronate) into the anterior chamber.
between the iris root and the trabeculum on 360° combined with goniosynechialysis. The same surgical procedure was performed 7 days later in the left eye. Surgery in both eyes was uneventful. The spherical dioptric power of the IOLs was selected to reach a plano-target on both eyes based on the Universal Barrett II Formula. A pre-loaded, single-piece aspheric monofocal hydrophobic acrylic lens (Artis® PL E, Cristalens Industrie, Lannion, France) (+23.0 D) was implanted in the right eye and +22.5 D in the left eye. Post-surgical follow-up examination was performed the next day, then again at 7 days, 1 month, and 2 months later. Follow-up therapy (pilocarpine 2% 3 times a day in both eyes) was initiated on postoperative day 7.

Results

Mild corneal edema with endothelial striae developed the day after both procedures. The anterior chamber was deeper in both eyes (Van Herick grade 2), the pupils were fixed, the IOLs were in place and centered in the capsular bag, the IOP was 16 mmHg in the right eye and 13 mmHg in the left eye, visual acuity was HM in the right eye and 20/30 Snellen in the left eye. Examination on postoperative day 7 revealed a clear cornea in both eyes, unresponsive pupils in both eyes, IOP was 16 mmHg in the right eye and 12 mmHg in the left eye, visual acuity remained HM in the right eye and 20/20 Snellen in the left eye. Fundoscopy and OCT of the macular region and optic nerve were similar to the pre-operative values. At 1 month postoperative, visual acuity and ophthalmological measurement remained unchanged since the previous visit; IOP was 11 mmHg in the right eye and 16 mmHg in the left eye. The endothelial count revealed a density of 1986 cells/mm² in the right eye and 2328 cells/mm² in the left eye; no guttae were present on the scans.

At 2 months postoperative, the anterior chamber was deep (Van Herick grade 2), the pupils were unresponsive in mild mydriasis. The IOP was within the normal limits (OD 15 mmHg, OS 12 mmHg). Visual acuity remained HM in the right eye and 20/20 Snellen in the left eye. Dynamic gonioscopy showed bilaterally a detectable Schwalbe’s line 360°, with a visualizable anterior trabeculum and spotty synechiae (Shaffer gonioscopy grading system 2; Spaeth gonioscopy grading system B 20 plateau configuration). The patient was referred to our tertiary Glaucoma Unit for periodic follow-up visits.

Discussion

The pathophysiology of PACG was substantially multifactorial in this case. While pre-existing anatomical characteristics constituted a substrate for the bilateral angle closure, it was ultimately triggered by medications, prone position, and hypoxia during hospitalization for COVID-19 treatment. The administration of norepinephrine (adrenergic agonist) and rocuronium bromide (muscle relaxant) is a known cause of mydriasis. Emotional stressful situations, such as ICU stay, are another cause. Such events draw the ciliary body of an eye with a plateau iris configuration towards the trabeculum, eventually obstructing the angle. Moreover, prone position is known to shift the anterior segment structures (lens, ciliary body, iris) forward, resulting in additional approximation of the iris towards the iridocorneal angle and an additional trigger for acute primary angle closure (APAC). Several hypotheses have been advanced to account for its occurrence. As a general observation, prone position is known to reduce anterior chamber depth due to the pressure of the vitreous body and the lens towards the cornea. Also, vascular alterations, particularly in venous drainage, may raise the IOP in the prone position. These factors increase the risk of APAC consequent to either plateau iris syndrome or pupillary block. In plateau iris syndrome, a shallower anterior chamber in conjunction with prolonged mydriasis can lead to angle closure via an “angle crowding” mechanism, in which the peripheral iris is pushed against the trabecular meshwork.

In this patient, hypoxia due to obstructive pneumonia and systemic hypotension further contributed to making the optic nerve of the right eye more vulnerable, ensuing in severe progression of visual impairment. Systemic hypotension itself may reduce ocular perfusion pressure (i.e. ocular perfusion pressure = mean arterial pressure – IOP). Prolonged systemic hypotension (treated with norepinephrine for 37 days) together with concurrent ocular hypertension reduced the ocular perfusion pressure. Furthermore, the persistently low O₂ pressure (50 mmHg at intubation and remaining low for weeks before returning to normal) induced a state of general hypoxia. Systemic hypoxia can cause irreversible damage to the optic nerve and the ganglion cells through multiple mechanisms such as increased oxidative stress, mitochondrial dysfunction, and activation of apoptosis pathways. While it is difficult to quantify the extent of damage to the optic nerve and the ganglion cells by each of these elements separately, they were all involved in increasing vulnerability to hyperbaric damage. In the clinical course of APAC, symptoms are usually perceived as strongly suggestive and are the reason why patients seek ophthalmic attention. In the present case, however, the anesthesia and the sedation made it difficult to interpret the signs and symptoms, resulting in delayed diagnosis and perpetuation of the damage. In the visual damage of APAC there is a stronger correlation with the duration of the attack than with the IOP. The anesthesiologists who examined the eyes of the patient recorded anisocoria and fixed pupils twice (the pupil of the right eye was more dilated than that of the left eye). A CT imaging study was ordered to check for suspected brain abnormalities.
The anisocoria and the fixed pupils probably were signs of APAC misinterpreted as neurological findings. UBM during diagnosis helped to clearly identify the type of angle closure, the iris conformation, and the morphology of the ciliary body and the ciliary sulcus. Based on the UBM findings effective treatment was initiated. The pathological mechanism behind PACG due to plateau iris configuration would have precluded Yag-laser iridotomy as it could not solve the iris-trabeculum apposition. Phacoemulsification and goniosynechiation are associated with high failure rates in advanced glaucoma and plateau iris configuration, and combined glaucoma and phaco surgeries are recommended instead. Phacoemulsification and goniosynechiolysis was selected as a standalone surgery because of the minimal residual visual function (HM) in the right eye in this case and because a more invasive procedure would have unnecessarily exposed the patient to complications. Glaucoma surgery on the right eye was not contemplated due to the absence of morphological and functional glaucomatous damage.

A pre-loaded, single-piece monofocal hydrophobic acrylic IOL was chosen based on its safety profile instead of a presbyopia correcting IOL because of the risks associated with these technologies in a monocular patient (e.g. incomplete neuro-adaptation, IOL calculating errors, ocular comorbidities). The IOL design took into account less IOL manipulation, with less risk of endothelial cell depletion due to the reduced anterior chamber depth in both eyes. The IOL was selected to ensure safe injection through a 2.2-mm tunnel and easy positioning and stability in the bag. The Artis® PL E is designed to be injected through a 1.8-mm incision, and the four closed haptics can be rotated clockwise and anti-clockwise during surgery while centering and positioning the lens.

The take-home message is that heightened attention to the trigger mechanisms for PACG and its prevention is warranted in ICU patients. Numbering among the risk factors are therapeutic measures and the general medical conditions of such patients. Early detection of PAC in ICU patients is fundamental for initiating early treatment and preserving their visual function. Detecting suspected PAC in the ICU would involve gonioscopy with an indirect ophthalmoscope on every bedridden patient, which is clearly unfeasible in such a busy clinical setting. Instead, taking accurate ophthalmic history with a focus on subjective and familiar predisposition to PAC is far more doable. We identified in anisocoric pupils the manifestation of APAC that was erroneously interpreted as a neurological sign. While it is difficult to suggest a protocol for managing this kind of situation, prompt ophthalmological evaluation in a patient with anisocoric pupils, before ordering a CT scan, seems to be both effective and straightforward. Instructing the ICU medical staff on how to perform digital measurement of IOP in patients presenting signs of PAC (conjunctival redness, anisocoria, etc.) could be another option when an ophthalmic consult is not readily available.

Authors’ contributions
Guido Barosco: data acquisition, manuscript preparation; Roberta Morbio: data acquisition; Francesca Chemello: manuscript preparation; Roberto Tosi: data acquisition; Giorgio Marchini: data acquisition, manuscript preparation.

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Informed consent
Informed consent was obtained from the subject.

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