A COVID-19-Related Retinopathy Case Report

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Abstract
The recent outbreak of the severe acute respiratory syndrome coronavirus-2 has been declared a worldwide pandemic by the WHO. Within various multi-organ involvements, several ocular manifestations have been described. We report the case of a patient diagnosed with COVID-19 who presented with a progressive increase of bilateral cotton wool spots over a 1-week period, despite quick and complete recovery of systemic signs of the disease and no ocular symptoms. We followed the evolution of such lesions over a 3-month period. Here, we underline the importance of retinal screening even if no ocular symptom is reported. Furthermore, we demonstrate the essential role of fundus examination as a reflection of systemic vascular changes.

Introduction
In December 2019, a new, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spread worldwide leading in the early 2020 to a pandemic disease named coronavirus disease 2019 (COVID-19) [1]. COVID-19 appears to involve multiple organ systems with pathological manifestations including the heart, kidney, and brain [2–5].
Retinal findings following infection with SARS-CoV-2 have been described and the presence of cotton wool spots (CWS) reported in several cross-sectional studies [6–10]. The pathophysiology, incidence, and the temporal behavior of the CWS remain unclear. We report a case of a patient infected by SARS-CoV-2 presenting with CWS that increased in number and size during follow-up.

**Case Description**

A 46-year-old Caucasian man was admitted to the Geneva University Hospitals with acute respiratory symptoms over 3 days and a positive RT-PCR test for COVID-19. He was previously in excellent health with no preexisting comorbidities such as obesity, cardiovascular disease, diabetes, or any other systemic disease that could affect retinal vasculature. He had no previous ophthalmic history. At admission, he presented with an oxygen saturation of 93%, which required supplementation at a flow rate of 2 L/min via nasal cannula. He complained of shortness of breath, fatigue, and headache. His systemic blood pressure was 130/90 mm Hg with a heart rate of 77 beats/min. His body temperature was 38.1°C. No other systemic symptoms nor ophthalmic complaints were reported.

A complete blood test revealed elevated D-dimer levels (675 ng/mL; normal <500 ng/mL), raised fibrinogen levels (7.8 g/L; normal 2–4 g/L), and elevated CRP (114 mg/L; normal <10 mg/L). Hemoglobin and complete blood count were normal. Serum electrolytes showed mild hyperkalemia (5.2 mmol/L; normal 3.6–4.6 mmol/L) and urine function showed decreased creatinine levels (61 μmol/L; 62–102 μmol/L).

As part of a prospective, observational study taking place at the Geneva University Hospitals in conjunction with the Clinical Eye Research Centre Adolph de Rothschild, the patient underwent wide field color fundus photography in both the eyes (Optos, Daytona; Optos PLC, Dunfermline, UK) at admission. Despite no visual symptoms, fundus photography revealed two CWS in the posterior pole of his left eye (Fig. 1). No such lesions were present in the right eye (not shown). Both fundi photos revealed diffuse arteriolar vasoconstriction.

Within the adopted protocol of COVID-19 patients, following the guidelines of the Recovery Collaborative Study Group [11] and the institutional recommendations, intravenous dexamethasone (6 mg daily) was administered immediately after admission and continued for 4 days in total. On the fourth day, the patient improved significantly and could be discharged with an oxygen saturation of 98%. All therapy was discontinued. Blood workup on discharge revealed persistent elevated CRP and potassium levels but both were remarkably decreased since the admission day. CRP decreased from 114 mg/L to 35.5 mg/L and potassium from 5.2 mmol/L to 4.7 mmol/L. Other laboratory analyses were within normal range.

**Fig. 1.** Color fundus photography (Optos, Daytona; Optos PLC) of the left eye at admission. Two isolated CWS are visible at the posterior pole (white arrows), indicating focal ischemia at the inner retinal layers. The blue arrow indicates an artefact due to light reflection. There was also evidence of diffuse arteriolar vasoconstriction.
Seven days after the first fundus examination we performed a full ophthalmic evaluation with fundus imaging including an optical coherence tomography (OCT) and fundus photography (Topcon DRI OCT Triton, Topcon, Corp., Tokyo, Japan). Best-corrected visual acuity was 20/20 in both eyes. Anterior segment examination was unremarkable with an intraocular pressure of 14 mm Hg in each eye. The left eye showed two additional, isolated CWS not present at admission (Fig. 2). OCT B-scan through one CWS showing thickening of the inner retinal layers indicating accumulation of axoplasmic debris and intracellular edema within the retinal nerve fiber and ganglion cell layers (Fig. 3). The fundus examination of both eyes showed the same diffuse vasoconstriction as during the first examination.

Three months after the initial examination, a further follow-up was performed. Best-corrected visual acuity was 20/20 in both eyes and the anterior segment examination and intraocular
pressure were unremarkable. Fundus examination of the left eye showed complete resolution of isolated CWS; however, diffuse arteriolar vasoconstriction could still be recognized as seen at admission, 3 months earlier (Fig. 4). The right eye showed the same diffuse vasoconstriction (not shown). OCT B-scan through the same CWS as in Figure 3 shows a hyperreflective sign associated to the median layers neuronal cell loss (bipolar or amacrine cells) which correspond to disruption of the inner retinal layers previously occupied by the CWS (Fig. 5).

Fig. 4. Color fundus photography (Topcon DRI OCT Triton, Topcon, Corp.) of the left fundus 3 months after admission. All CWS regressed with no visible sign of retinopathy.

Fig. 5. Composite photo at 3 months after admission. Color fundus photo (top left) showing total regression of all four CWS at the posterior pole. Red free photo with no lesions (top center). OCT B-scan through the same area previously occupied by the CWS 3 months earlier, showing a hyperreflective sign associated to the median layers neuronal cell loss (bipolar or amacrine cells) corresponding to disruption of the inner retinal layers (bottom). Color-coded thickness map of the retina showing normalization with regression of all 4 CWS (top right).
Discussion

We report a case of unilateral COVID-19-related retinopathy with ongoing formation of CWS in an otherwise healthy 46-year-old patient. Augmenting CWS occurred despite steroid and oxygen therapy and favorable and quick recovery of systemic symptoms and signs.

COVID-19 is now recognized as a multi-organ disease that affects endothelial cells across vascular beds of different organs. It is suggested that the virus SARS-CoV-2 infects the host by using the angiotensin converting enzyme 2 (ACE2) receptor to which it has a particularly strong affinity and which is expressed not only in the lung, heart, kidney, intestine but also in the retina [12–14]. SARS-CoV-2 attaches to the ACE2 via its spike protein [15].

Most patients suffering from COVID-19 described in the literature presented with several comorbidities including arterial hypertension, diabetes mellitus, coronary artery disease, and chronic kidney diseases [10, 16]. The high prevalence of concomitant pathologies in these reported cases made it difficult to distinguish whether the CWS were related to COVID-19 or to the previous clinical status [16]. Our patient had no preexisting chronic diseases nor cardiovascular risk factors such as smoking or obesity.

CWS related to COVID-19 have been previously described [6–10], but their incidence, extent, size, and number appear to be more limited than in other retinopathies [10]. CWS are nonspecific, acute retinal lesions representing a focal ischemic process due to an occlusion of a terminal retinal arteriole. Local anoxia causes accumulation of axoplasmic and cytoplasmic debris in the retinal nerve fiber layer due to obstruction of orthograde or retrograde axoplasmic transport [17] associated to intraneuronal edema.

The localization of CWS to the posterior pole in COVID-19-related retinopathy may suggest an occlusion either of the peripapillary capillary network or their feeding arterioles. The peripapillary capillary network extends 2 and 4 disc diameters nasal and temporal to the optic disc, respectively, and measures up to 45 μ in diameter, suggesting an involvement of only the smallest terminal capillaries.

The exact physiopathology, incidence, and behavior of the CWS found in relation with COVID-19 is not yet well understood. One of the explanation could be a vascular obstruction caused by a direct viral tissue injury and infiltration of the endothelial cells via the ACE2 receptor. ACE2 receptor are expressed in multiple neuro-retinal cells including the retinal ganglion cell layer, inner plexiform layer inner nuclear layer, and photoreceptor outer segments [18].

The resulting cytokine release might cause further direct injury with release of inflammatory and apoptosis-inducing mediators. These could lead to localized microvascular inflammation, a form of vasculitis or an immune-complex deposition on vessel walls, similar to findings in human immunodeficiency virus [10], triggering endothelial activation, vasodilation, and prothrombotic conditions. Of notice, our patient did not show any significant signs related to vasculitis; indeed, the fundus examination did not reveal vascular sheathing, vitritis, or hemorrhages, nor did we observe vasodilation of retinal arterioles. Fluorescein angiography, which is typically performed to confirm the presence of these signs, would have confirmed our findings but was not performed.

Another explanation could be a secondary hypercoagulable state caused by disproportionate production and deposition of fibrin clots in small and midsize vessels that could lead to occlusion of retinal precapillary arterioles with CWS formation. Such findings have been reported in disseminated intravascular coagulopathy-like syndrome [16]. Indeed, our patient presented at admission signs of hypercoagulability with significantly increased levels of D-dimer, fibrinogen, and CRP. D-Dimer elevation, a marker of thrombus formation, has been reported to be one of the most frequent laboratory findings in COVID-19 patients [19]. In addition, the clinical presentation of CWS in our case resemble those found in Purtscher-like retinopathy (PLR), a syndrome related to a hypercoagulability state related to various systemic diseases [19].
PLR is usually characterized by bilateral posterior pole CWS with or without retinal bleeds. Hyperbaric oxygen combined with systemic steroids have been shown to lead to a favorable outcome in PLRs [20]. It is possible that in our patient the isolated CWS without hemorrhages was related to the immediate intravenous steroid administration and oxygen supplementation following the protocol to all COVID-19 patents at our institution based on the recent results of the RECOVERY study [11]. It is therefore possible that COVID-19-related retinopathy could be part of the PRL-like syndrome induced by a state of hypercoagulability. A recent article reported a significant correlation between the decrease in superficial retinal vascular density among COVID-19 patients measured with OCT-angiography (OCT-A) and the levels of D-dimers [21]. While the authors concluded that these findings were related to a hypercoagulability state, they did not account for the fact that over 70% of the patients included in their study suffered from various comorbidities (arterial hypertension, diabetes, dyslipidemia) which could have influenced the retinal vascular presentation. Indeed retinal vascular density is modified in hypertensive patients as compared to healthy subjects [22]. In another study performing OCT-A on patients fully recovered from COVID-19, the authors suggest that persistent retinal vascular changes could be explained by thrombotic microangiopathy [23].

Our patient had no cardiovascular comorbidities prior to COVID-19, no diabetes, and was a non-smoker. We can therefore conclude that the retinal findings in his case were only related to COVID-19.

Finally, CWS may arise in COVID-19 as a result of hemodynamic disturbance causing diffuse or focal vasospasm. This condition could be induced either by hypoxia related to the acute respiratory distress or to an acute rise in blood pressure in the early phase of the disease. Capillary closure can also be related to smooth muscle contraction of the endothelial cells and pericytes or by vascular collapse due to localized hemodynamic imbalances [24], revealing a diffuse arteriolar vasoconstriction in both eyes that seems to persist over the 3-month follow-up period. Interestingly, our patient has no cardiovascular disease and did not report any previous high blood pressure. On admission, his BP was in the normal range. Whether vascular changes following the acute respiratory failure in COVID-19 may simulate a chronic condition such as sleep apnea is questionable. Sleep apnea is often associated with systemic hypertension contributing to retinal arteriolar vasoconstriction. In this regard, focal anoxia in some vulnerable terminal arterioles could explain the occurrence of only focal CWS. However, sleep apnea is a chronic condition and the vasoconstriction needs time to form progressively. In accordance with our results is the recent finding of a significant reduction in vessel density of the superficial and deep capillary plexus in patients who had recovered from COVID-19 as compared to those in healthy subjects [20]. The natural characteristic life cycle of CWS goes from an initially fluffy white focal opacity resolving over 10 days to duller, fragmented white patch before disappearing by 3–8 weeks and resulting in an apparently normal-looking transparent retina on ophthalmoscopy examination [25].

In our patient, the first CWS were detected on the day of admission, approximately 3–4 days after the initial respiratory symptoms. Their fluffy appearance leads to believe that they were in their early stage of the cycle. The fact that their number and size increased during the first week despite steroid and oxygen therapy and despite significant improvement of systemic signs may suggest a delay between hematological parameters and the behavior of the capillary vascular bed. Whether an even more increased number of CWS would have been found without applied therapy is unknown. Unfortunately, even though a fluoangiography would have helped to exclude other peripheral diffusions or occlusions, or vascular abnormalities in the eye with no lesions, we were not able to perform such exam due to the limited resources. Since the eye allows a direct visualization and quantification of the vasculature, our findings could represent signs of vascular involvement in other organs besides the eye and therefore a new biomarker related to COVID-19.
In conclusion, we report a case of COVID-19 with retinal manifestations in form of CWS that increased with time despite steroid and oxygen therapy and resolution of all systemic symptoms and signs. We discuss several hypothesis and factors that could lead to formation of CWS. While a multifactorial mechanism is possible, we postulate that these vascular changes could arise either from microvascular inflammation, micro-embolic phenomena secondary to a hypercoagulability state induced by COVID-19, or a dysregulation in the hemodynamic state. Additional studies on COVID-19 patients that include fluorescein angiography may provide more insight into mechanisms leading to CWS formation.

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Statement of Ethics

Swiss Ethics Committees approval was obtained. ID reference number is 2020-02873. Date of approval was October 14, 2021. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Eleonora Riotto did the data collection, and writing. Vladimir Mégevand and Alexis Mégevand did the data collection. Gordana Sunaric Mégevand and Alexandros Stangos created the project and helped in the writing process. Jérome Pugin helped with the project organization. Christophe Marti and Constantin Pournaras helped with the writing.

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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