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Case Report

Different Cases, Different Manifestations of Post-COVID-19 Retinal Artery Occlusion: A Case Series

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Abstract

Coronavirus disease 2019 (COVID-19) is a procoagulant disease that increases the risk of clinically evident thrombotic complications. Herein we present 3 cases with different retinal artery occlusions that emerged soon after the diagnosis of COVID-19. The first patient had central retinal artery occlusion (CRAO) that resulted in visual loss in one eye. The second patient had inflammatory peripheral retinal artery occlusion, vasculitis, and uveitis which did not affect vision. The third patient presented with CRAO following the progression from orbital cellulitis to orbital apex syndrome. Interestingly, CRAO progressed to internal carotid artery occlusion in this case within days and resulted in monocular visual loss. Variations in the underlying pathophysiology and the characteristics of individual immune responses in patients with COVID-19 may be factors that determine differences in clinical manifestations. This article aims to describe different presentations of COVID-19-related retinal artery occlusions and discuss possible pathophysiological aspects.

Keywords: COVID-19, retinal artery occlusion, SARS-CoV-2

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel member of the human coronaviruses and causes coronavirus disease 2019 (COVID-19).[1] It has the potential to affect various organs and systems within the body. Ocular involvement of the disease is potentially possible, though it is not known when, why, in whom, how, and to what extent SARS-CoV-2 will affect the ocular tissues.[2]

COVID-19 is known to be a procoagulant disease that increases the risk of clinically evident thrombotic complications.[3,4] Recently, it has been published that 42.7% of cases with SARS-CoV-2-associated neurological complications presented with ischemic stroke.[5,6] By definition, retinal artery occlusion represents end-organ ischemia and is analogous to terminal branch occlusion in cerebral stroke.[7] Although the overall incidence of arterial thrombosis in COVID-19 has been reported to be lower than that of venous thrombosis (3.7% vs. 25%), the number of retinal artery occlusion cases in the literature is close to that of retinal vein occlusions.[8,9]

However, the components involved in the ocular thromboembolism process, the mechanism of interaction, and the clinical findings have not yet been adequately defined. Herein we aim to report three cases with different types of retinal artery occlusions secondary to COVID-19 and to discuss possible pathophysiological aspects. Written informed consent for publication of the clinical details and/or clinical images have been obtained from all patients in this study.

Case Reports

Case 1

A 48-year-old woman presented with blurry vision in the right eye that started the day before. The patient had been diagnosed with COVID-19 fifteen days earlier and treated with favipiravir according to the Ministry of Health policy at that time. As in all cases in this series, COVID-19 was diagnosed by a real-time reverse transcription polymerase chain reaction (RT-PCR) swab test upon the presence of related symptoms. Her past medical history was insignificant. Pulmonary involvement of SARS-CoV-2 was not found. Outpatient treatment was deemed sufficient for the patient and hospitalization was not required during or after the quarantine period. The patient reported that she had no severe side effects of the disease or treatment and her symptoms of fatigue and fever resolved within a week. Fourteen days after the initial diagnosis of COVID-19, her vision diminished in the right eye.

At presentation, best corrected visual acuity (BCVA) was hand motion in the right eye and 20/20 in the left eye. Anterior segment examination and intraocular pressure were within normal limits in both eyes. Fundus fluorescein angiography (FFA) showed signs of delayed arterial perfusion, poor perfusion in the retinal artery, and prolonged arteriovenous transit time, while optical coherence tomography (OCT) (Heidelberg Engineering Gmbh, Heidelberg, Germany) demonstrated increased reflectivity and thickness of the inner retina suggesting central retinal artery occlusion (CRAO) in the right eye. However, the left eye was quite normal. Systemic workup showed elevated levels of D-dimer, fibrinogen, factor VIII, and von Willebrand factor, while antithrombin was decreased (**Figure 1**).

Anterior chamber paracentesis was performed on the day of presentation and the patient was referred to hyperbaric oxygen treatment for 21 days. However, at 10 months after presentation, her BCVA is still hand motion in the right eye and 20/20 in the left eye. OCT shows significant inner retinal atrophy in the right eye. There is no sign of neovascular glaucoma. The patient did not have any systemic complications related to COVID-19 during follow-up.

Case 2

A 46-year-old woman presented with sudden-onset concentric visual field loss in both eyes. She had been diagnosed with COVID-19 ten days earlier and received favipiravir treatment. Pulmonary involvement of SARS-CoV-2 was not detected at that time. Her BCVA was 20/20 in both eyes. Biomicroscopy showed that there were 1+ cells in the anterior chamber and vitreous of both eyes. Intraocular pressures were within normal limits. Funduscopic examination revealed a partial macular star in the right eye and bilateral peripheral vascular sheathing suggesting retinal vasculitis (**Figure 2**). Multiple areas of arterial

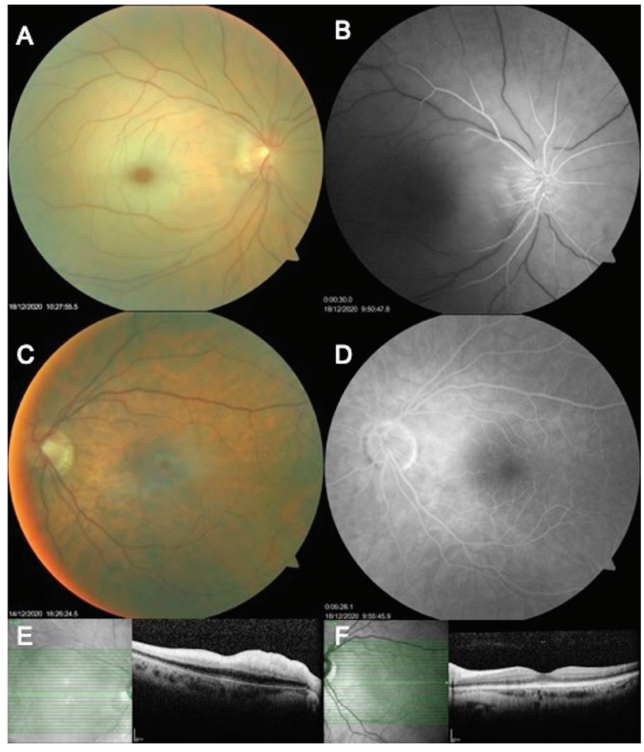

Figure 1. Fundus photography, fundus fluorescein angiography (FFA), and optical coherence tomography (OCT) of patient 1 (48-year-old female). FFA showed signs of longer arterial perfusion time, poor perfusion in the retinal artery, and delayed arteriovenous transit time, while OCT demonstrated increased reflectivity and thickness of the inner retina suggesting central retinal artery occlusion in the right eye

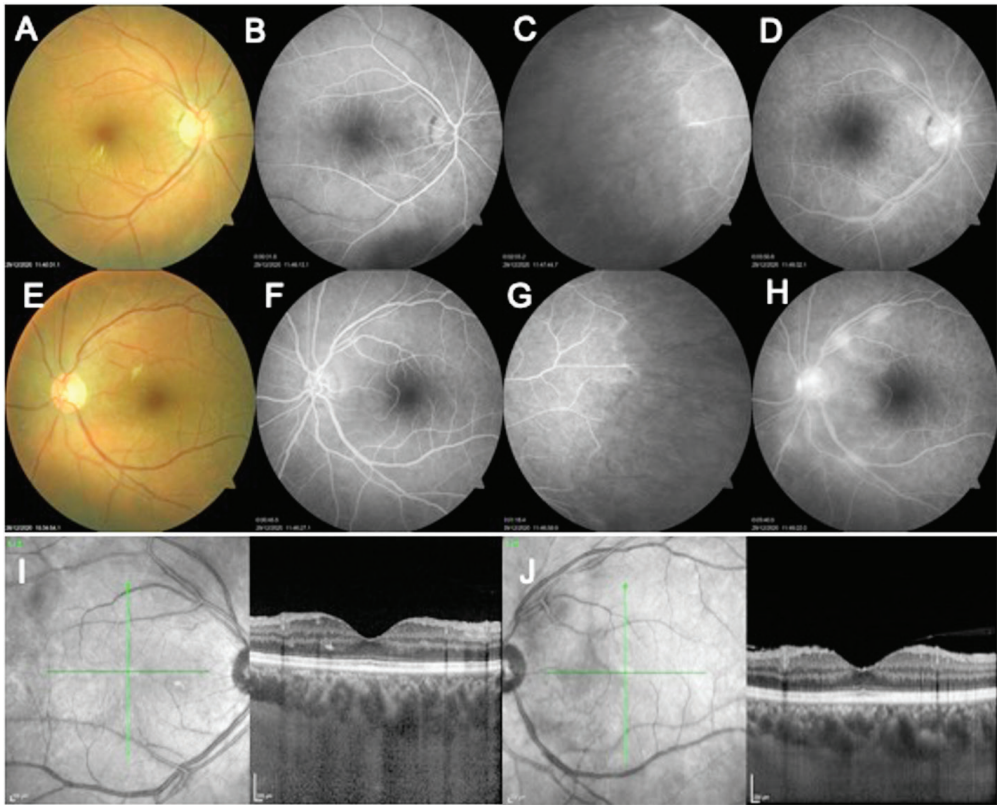

Figure 2. Fundus photography, fundus fluorescein angiography, and optical coherence tomography images from patient 2 (46-year-old female). She had mild uveitis, retinal vasculitis in the posterior pole, and peripheral retinal artery occlusion in both eyes. A-D and I show the right eye while E-H and J show the left eye

wall hyperfluorescence were present in the posterior pole and peripheral retina in both eyes, while capillary dropout extending from the equator to the ora serrata was visible on FFA bilaterally (**Figure 2**). There were no signs of retinitis.

Her past medical history was unremarkable for systemic diseases. Systemic and ocular workup was initiated for further investigation. She had no complaints other than intermittent non-specific mechanical back pain. No recent or past hearing loss or central nerve system dysfunction were present. The patient had no history of oral or genital aphthae. Diagnostic work-up for retinal vasculitis and/or vascular occlusion including hypertension, systemic lupus erythematosus, Susac's syndrome, granulomatosis with polyangiitis, Behçet's disease, tuberculosis, and thrombophilia all resulted negative. Flow parameters of the carotid arteries and the ophthalmic arteries were normal on Doppler ultrasonography. Levels of D-dimer and fibrinogen were also found to be within normal limits.

The patient was started on high-dose methylprednisolone, with azathioprine added in the second week of steroid therapy. Due to the persistence of peripheral retinal ischemia, panretinal laser was applied to the ischemic areas two months after the onset of symptoms. The patient is in the ninth month of follow-up and her BCVA is still 20/20 in both eyes. Optic disc hyperfluorescence is present in both eyes on FFA. Reportedly, the patient had no health-related quality of life challenges after COVID-19.

Case 3

Consultation was requested for a 66-year-old man in the emergency department complaining of vision loss in his left eye. He had a history of positive COVID-19 PCR test 22 days prior to presentation and was hospitalized for 15 days due to bilateral peripheral ground glass and consolidative pulmonary opacities suggestive of pulmonary involvement. No signs or symptoms of pulmonary embolism were detected and intensive care was not needed during hospitalization. In accordance with Ministry of Health policy, he was discharged after treatment.

Within the week following his discharge, the patient developed pain and proptosis of the left eye with eyelid edema and ptosis. At 1 week after discharge, he presented with complaints of decreased vision for 2 days. On ophthalmological examination, his BCVA was 20/20 in the right eye and light perception (LP) in the left eye. Ocular motility, lid function, and corneal reflexes were normal in the right eye, but features of orbital cellulitis including ophthalmoplegia and relative afferent pupillary defect were noted in the left eye (**Figure 3**). The anterior segments were normal in both eyes, whereas CRAO was present in the left fundus. OCT revealed hyperreflectivity in the inner retinal layers. Consistent with non-perfusion, FFA displayed impaired chorioretinal filling even after 5 minutes (**Figure 4**).

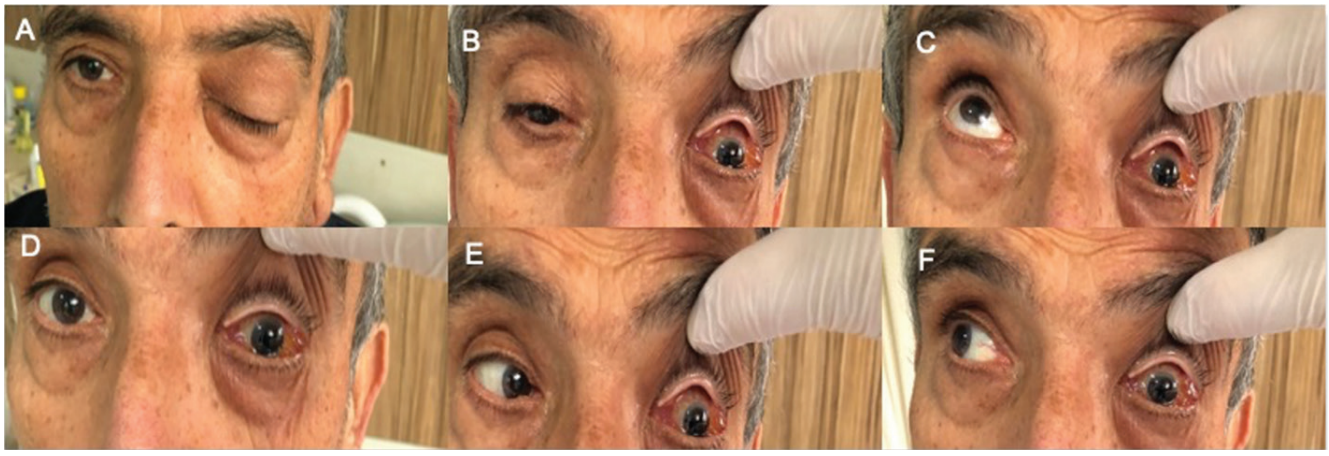

Figure 3. Patient 3 exhibited eyelid edema (A), ptosis (A), and ophthalmoplegia (B-F) of the left eye

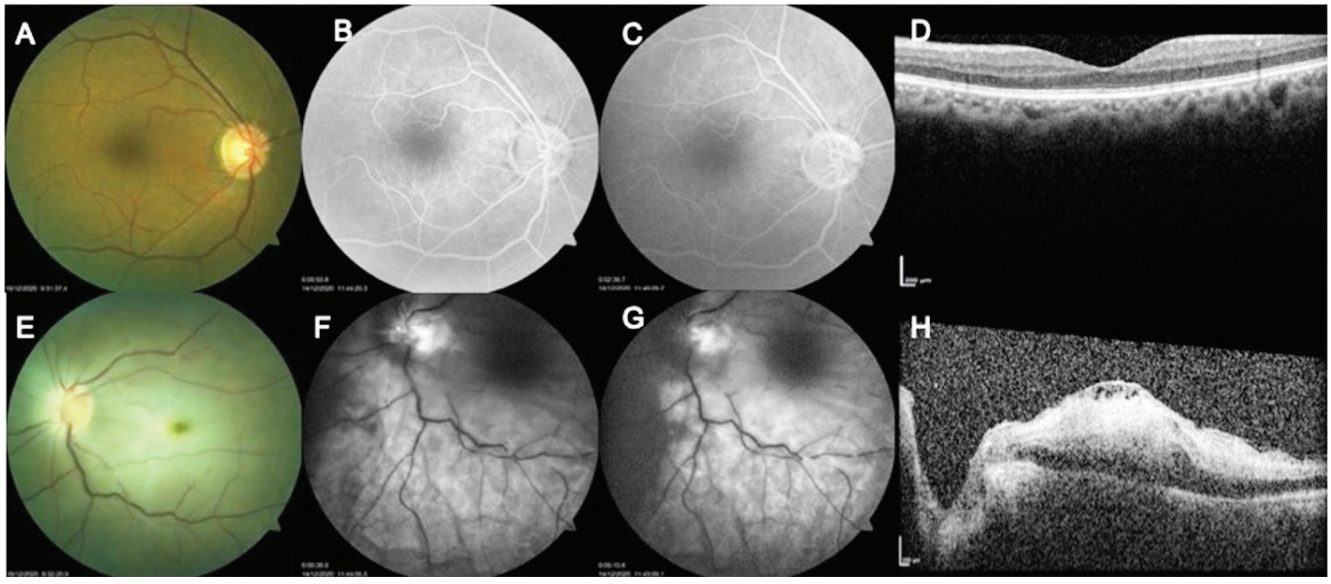

Figure 4. Fundus fluorescein angiography and optical coherence tomography findings in patient 3 (66-year-old male) indicated the presence of central retinal artery occlusion. A-D show the right eye while E-H show the left eye

The patient had type 2 diabetes mellitus and underwent coronary artery bypass surgery in 2004. The decision was made to hospitalize the patient for further investigation. There was no systemic abnormality in his physical examination, and no signs of necrotic lesions were observed in the oral examination. Consistent with left orbital apex syndrome, orbital magnetic resonance imaging (MRI) revealed preseptal and postseptal inflammation, prominent optic nerve edema, and severe restriction findings on diffusion MRI (**Figure 5A**). The appearance and intensity of brain parenchyma were normal on cranial MRI. Laboratory tests showed elevated levels of D-dimer, fibrinogen, factor VIII, and von Willebrand factor and attenuated levels of antithrombin. The patient was started on amoxicillin-clavulanic acid and 1 mg/kg prednisolone with tight blood sugar control. Anticoagulants were not administered at that time. One week after the onset of ocular symptoms, the patient experienced sudden-onset weakness, numbness, and difficulty with speech and understanding which resolved within 24 hours.

Two days later, the patient exhibited right hemiparesis involving the arm. On cranial MRI, newly developed distinct diffusion-restricting areas suggesting acute-subacute infarction were observed in the left frontal and parietal lobes (**Figure 5B**). Computer tomography angiography showed complete occlusion of the left internal carotid artery (ICA) (**Figure 5C**). No further endovascular intervention was considered as the left middle cerebral artery was recanalized with collaterals. The patient started physical rehabilitation for the paresis. At the time of writing, he is in the tenth month of follow-up and still has limited upper limb mobility and LP vision in the left eye. Ptosis of the left eyelid improved while ocular motility returned to normal.

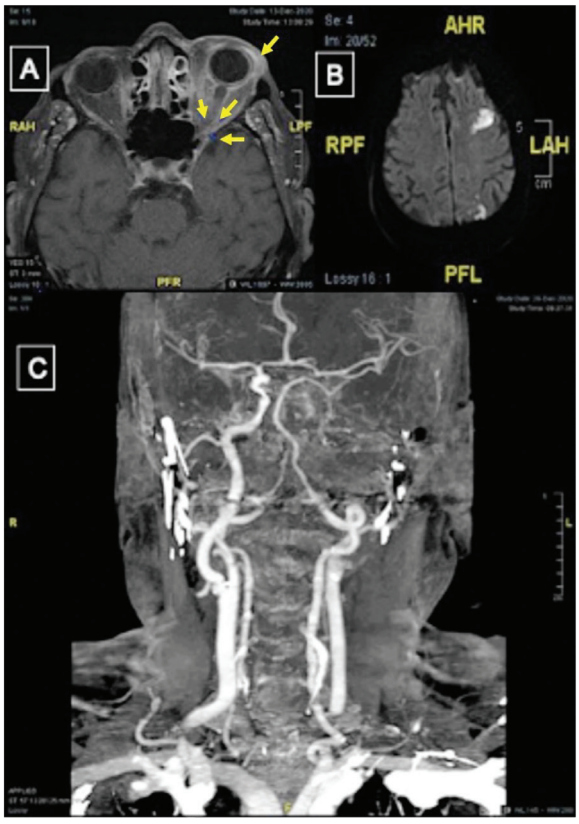

Figure 5. A) Preseptal and postseptal inflammation and prominent optic nerve edema in patient 3 at presentation are marked with arrows on orbital magnetic resonance imaging (MRI). B) On the ninth day of hospitalization newly developed distinct diffusion-restricting areas suggesting acute-subacute infarction were observed in the left frontal and parietal lobes on cranial MRI. C) Computed tomography angiography shows complete occlusion of left internal carotid artery on after the onset of right hemiparesis

Discussion

Growing evidence shows that macrovascular and microvascular thrombotic diseases may occur in the venous and arterial circulation of both hospitalized and ambulatory patients with COVID-19.[10,11,12] The question of whether thrombosis is specific to SARS-CoV-2 or is a pathway of the thromboinflammatory response to viral infection remains uncertain.[13] A recent autopsy study revealed that almost no organ within the body is spared of thrombosis.[14]

This case series highlights that retinal artery occlusions associated with SARS-CoV-2 may present with different features. Herein, isolated microvascular occlusion was observed in the first two cases. The first case was a routine case of CRAO which seems to be of thromboembolic origin. However, the second patient had inflammatory peripheral retinal artery occlusion, vasculitis, and uveitis. The third case featured CRAO originating from the progression of orbital cellulitis to orbital apex syndrome. Interestingly, this microvascular occlusion progressed to macrovascular (ICA) occlusion within days.

In COVID-19, variations in the underlying pathophysiology and characteristics of individual immune responses may be factors that determine differences in clinical manifestations.[15] Although the pathophysiological mechanism of thromboembolic complications in the ocular vasculature has not been clearly established, the coagulopathy mechanisms proposed in SARS-CoV-2 infection may be relevant.[16,17] Evidence from the literature shows that SARS-CoV-2 infects vascular endothelial cells via ACE2, which is highly expressed in endothelial cells and pneumocytes. Basically, destruction of ACE2 receptors has been associated with increased levels of reactive oxygen species, induction of fibrosis, hypertrophy, and inflammation.[18] The resulting endothelial dysfunction and subsequent potentiation of the renin-angiotensin system reduces anticoagulation and fibrinolytic activity. The emergence of extensive hypercoagulation, diffuse intravascular thrombosis, and secondary fibrinolysis may lead to microvascular and macrovascular complications in COVID-19.[19] Hypothetically, the clinical picture may progress to retinal artery occlusion, as in the first case, when the pathology is limited to the ocular microvasculature.

On the other hand, SARS-CoV-2 can also stimulate the innate immune system to participate in thrombosis. Essentially, immune cells, inflammatory cytokines, and pathogen-associated molecular patterns induce the formation of thrombi consisting of fibrin, monocytes, neutrophils, and platelets.[20,21,22] Although immunothrombi initially promote pathogen recognition and serve as a protective barrier against pathogen invasion, they may become maladaptive and injurious to tissue and organ perfusion in time.[20,23,24] Alveolar immunothrombosis has been proposed as a mechanism to limit dissemination of SARS-CoV-2 outside the alveoli.[14] The peripheral retinal artery occlusion in our second case may have been caused by a similar mechanism or from occlusive retinal vasculitis which may have been triggered by or as a response to COVID-19. Cases of COVID-19-related uveitis of varying severity have been reported in the literature, but the presence of mild uveitis, retinal vasculitis, and peripheral retinal artery occlusion has not been reported before.[25]

In the third case, the possible underlying pathophysiology seems somewhat complex. The arterial occlusion may have been caused by the direct thrombotic effect of COVID-19.[16,17] In this case, as in our first patient, the increase in D-dimer, fibrinogen, factor VIII, and von Willebrand factor and the decrease in antithrombin levels seem to support this suggestion. However, other mechanisms may have been involved as well. In this context, progression of orbital cellulitis to orbital apex syndrome may be the key factor. Progression of orbital cellulitis to orbital apex syndrome has been reported before in patients with COVID-19, which is congruent with our third case.[26] In our opinion, further invasion of inflammation may have triggered retrograde spread to the cavernous sinus and caused involvement of the vascular ICA wall. The resulting stenosis may have caused occlusion of the ICA in this third case.

In summary, all these different clinical courses depicted above emerged soon after the diagnosis of COVID-19 and had variable visual prognoses and possible mechanisms of action. In addition to one case without vision loss, two cases with devastating vision loss occurred in our series. There have been several recent reports of retinal artery occlusion associated with

SARS-CoV-2, ranging from isolated CRAO to ischemic stroke with CRAO and cilioretinal artery occlusion with paracentral acute middle maculopathy.[27,28,29] To our knowledge, this is the first case series to include cases of post-COVID-19 CRAO with different presentations. While the limited number of cases, the speculative nature of the available evidence, and the individual characteristics of patients preclude any firm conclusions, this study may help gain insight into a fairly new topic that is likely to have more facets and deeper connections.

Currently, the cause of microvascular or macrovascular thromboembolism in the ocular vasculature in patients with post-COVID-19, its mechanism of development, prognostic significance, and the necessity of prophylactic measures are still unclear. Prevention of irreversible visual loss depends mainly on suspicion and timely intervention. The importance of increasing awareness of ocular thromboembolic complications and reinforcing a multidisciplinary approach is obvious. Further studies on the propagation of ocular screening in patients with COVID-19 may help solve this inadvertent complication.

Ethics

Informed Consent: Each patient provided written informed consent for inclusion in this study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: Ö.Y., G.U.G., F.C., B.H., Design: Ö.Y., G.U.G., F.C., B.H., Data Collection or Processing: Ö.Y., G.U.G., B.H., S.D., Analysis or Interpretation: Ö.Y., G.U.G., F.C., B.H., S.D., Literature Search: Ö.Y., G.U.G., F.C., Writing: Ö.Y., G.U.G., F.C., B.H., S.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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