Case Report

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# Central retinal vein occlusion and occlusive vasculopathy at macula in a patient with recent COVID-19 infection

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**Abstract:**

We described a post-COVID-19 patient who presented with central retinal vein occlusion and macular ischemia. A 50-year-old male presented with decreased vision for a month in his right eye (RE). The patient had no systemic risk factors for vascular disease but recent COVID-19 infection. Fundus examination revealed dense intraretinal dot hemorrhages especially at macula and ischemia-related retinal whitening in the posterior pole in RE. Expanding of foveal avascular zone was also detected in optical coherence tomography angiography (OCTA) sections. After systemic steroid therapy, subretinal fluid resolved but visual acuity did not increase. Depending on the fundus fluorescein angiography and OCTA findings, clinical picture was compatible with previous central retinal vein occlusion with superimposed occlusive vasculopathy at macula. COVID-19 patients with visual problems must be considered with care in regard to thrombotic retinal diseases.

**Keywords:**

COVID-19, immune complex, inflammation, ischemia, retinal vasculitis

## Introduction

Wide clinical spectrum from asymptomatic disease to severe pneumonia in COVID-19 is observed in ongoing studies and clinical experience. Both severity of disease and location of infection can vary so extensively. The risk factors for severe disease and cytokine storm are main subjects of many clinical studies about COVID-19.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is not just a viral pneumonia agent; it also causes induction of inflammatory cascades and hypercoagulability state according to the recent reports.[1-3] Thromboembolic complications can occur in cases from severe to mild systemic presentations.[4,5] Similarly, thrombotic complications may appear during disease or after recovery.

Venous thromboembolism and pulmonary embolism (PE) are some of the most common complications for post-COVID-19 patients.[6,7] The incidence of PE and deep vain thromboembolism was around 20%–30% in critically ill patients.[1] Intermediate or therapeutic dose of low-molecular-weighted heparin was also suggested in this group.[8]

Thromboembolic complications of retinal vessels are also observed in post-COVID-19 patients. Inflammation of vascular endothelium and hypercoagulability state are possible reasons of these complications.

Herein, we report a case of central retinal vein occlusion (CRVO) with superimposed occlusive vasculopathy at macula in a patient recovered from COVID-19. We emphasize that COVID-19 may be a potential risk factor for retinal vascular occlusions probably due

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to immune complex activation, especially in patients without any other risk factors or systemic thrombotic diseases.

## Case Report

A 50-year-old male presented with decreased vision for a month in his right eye (RE). The patient described his first symptom as severe and painless vision loss after waking up. After this symptom, the patient had been admitted to the emergency service. After physical and ophthalmologic evaluation, CRVO had been diagnosed and only cranial magnetic resonance imaging and several blood tests had been obtained. No particular therapy had been given in this stage. Two days later, intravitreal Aflibercept had been applied just once in another center. Another ophthalmologist had applied periocular leech therapy for a possible anticoagulant effect 2 days after intravitreal injection. The patient did not benefit from any of these therapies and he was referred to our clinic.

Blood test results of the day when symptoms first started were reached from patient's medical records. In emergency service blood test results, full blood count, urea, and creatinine had been found within normal limits. D-dimer and PT were within normal range, PTT (20.3 s) was slightly below and lactate dehydrogenase (LDH) (222 U/L) was slightly above the normal limits. Protein C, protein S, anti-thrombin activity, and homocysteine levels were in normal limits.

During the examination in our clinic, the patient mentioned 1 week period of severe fatigue and myalgia at 2 weeks before the acute vision loss. COVID-19 had been diagnosed via nasopharyngeal SARS-CoV-2 polymerase chain reaction during that time. For confirmation of previous mild COVID-19, blood antibody test was performed and SARS-CoV-2 IgG was found positive. Best corrected visual acuity was counting fingers at 0.5 m in RE and 20/20 in left eye (LE). Anterior segment examination was within normal limits in both eyes. Intraocular pressure was 12 mmHg in RE and 16 mmHg in LE. Fundus examination revealed dense intraretinal dot hemorrhages in posterior pole, macular edema, disc pallor and diffuse retinal whitening at macula in RE. Perivascular sheathing in large vessels and macular veins represented occlusive vasculopathy in macula [Figure 1]. Fundus appearance of LE was normal [Figure 1]. Fundus fluorescein angiography (FFA) of RE revealed extensive capillary nonperfusion areas at macula and periphery compatible with CRVO with superimposed macular occlusive vasculopathy. Macular edema appearance and expanding of foveal avascular zone were observed. Retinal hemorrhages were also hypofluorescent. Hyperfluorescent aggregates and partial staining in

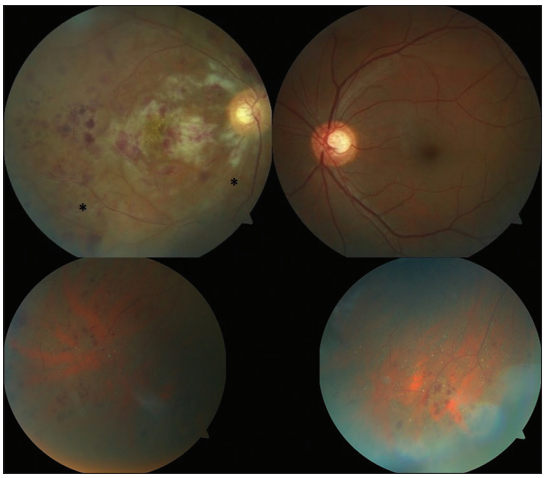

**Figure 1:** Color fundus photographs of macula and periphery of the right eye and macula of the left eye in the presentation. Dense cotton wool spots, microhemorrhages in macula and periphery, macular edema, disc pallor and retinal whitening were seen in right eye while left eye was normal. Vascular sheathing in macular veins and large vessels was labeled with asterisk (*).

vessel walls, especially in veins were deemed compatible with retinal vasculitis [Figure 2a]. Expanding of foveal avascular zone due to the occlusion of macular capillary plexuses was also detected in optical coherence tomography angiography (OCTA) sections [Figure 2b]. Macular edema, subretinal fluid and retina nerve fiber layer swelling were detected in spectral-domain optical coherence tomography (SD-OCT) [Figure 3a]. Possibly previous CRVO with superimposed occlusive vasculopathy at macula was diagnosed based on clinical picture and FFA findings.

The patient had no risk factors for retinal vascular occlusion such as diabetes mellitus, systemic arterial hypertension or hereditary coagulation disorders. Cardiology consultation with the examinations of 24-h Holter electrocardiography, carotid and vertebral artery Doppler ultrasound were all unrevealing. Rheumatology and Hematology evaluations were also unremarkable. Coagulation tests and rheumatic antibody panel were performed. Rheumatoid factor, anti-phospholipid IgG, anti-SS A, anti-SS B, anti-Scl 70, anti-CCP, anti-ds DNA, p- antineutrophil cytoplasmic antibodies (ANCA) and c-ANCA were found negative. Physical examination didn't reveal any finding for a rheumatologic disease. In coagulation tests, PTT was 19.2 s (below normal limits, normal range: 21–32), PT was 10 s (below normal limits, normal range: 10.4–15), d-dimer was 0.64 mg/L (slightly higher than normal limits) and LDH was 191 IU/L. Patient had no history of COVID-19 vaccination.

Systemic steroid therapy was applied for possible COVID-19 related occlusive vasculopathy and tapered in 3 months. After 3 months, VA was still counting fingers at 0.5 m. Complete resolution of macular edema and

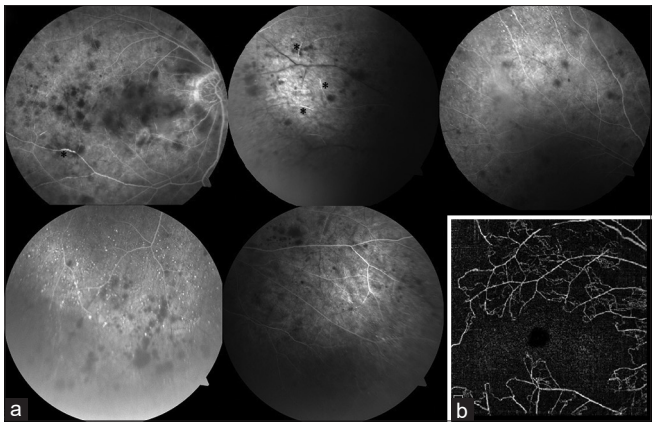


**Figure 2:** Fundus fluorescein angiography (a) and optical coherence tomography angiography (b) of the right eye. In fundus fluorescein angiography, severe macular ischemia, vascular wall staining, and hyperfluorescent vascular aggregates were seen. Vascular aggregates and perivascular staining were shown with asterisk (*). Expansion of foveal avascular zone in superficial capillary plexus layer was observed in optical coherence tomography angiography.

subretinal fluid was detected in SD-OCT. Total atrophy and thinning in fovea and loss of photoreceptor layer were also observed as a sequela secondary to severe vessel occlusion [Figure 3b]. Macular edema resolved and optic disc pallor was seen in fundus photography in last examination after treatment.

## Discussion

SARS-CoV-2 can cause different ocular manifestations. Retinal vascular complications were increasingly reported in COVID-19 patients in current literature.

Casagrande *et al*. detected SARS-CoV-2 RNA in retina of COVID-19 patients.[9] Angiotensin converting enzyme 2 (ACE-2) was accepted as the major receptor for entry of SARS-CoV-2 to host cell. ACE-2 was showed in retina, vitreous, aqueous humor and some other ocular tissues in recent reports, so ocular affinity of SARS-CoV-2 may be explained with expression of this molecule in ocular tissues.[10,11]

Increased pro-inflammatory cytokines at the stage of hematogenous dissemination of virus cause endothelial damage. ACE-2 expression in endothelium cells starts the inflammatory response in vascular structures. Endothelial damage can activate coagulation system via different pathways.[12] Endothelial dysfunction also contributes to thrombosis process due to reduced capabilities of fibrinolysis, vasodilatation and anti-aggregation. Endothelial cell damage causes thrombotic complications at clinical practice.[13]

COVID-19-related retinal vascular occlusion cases have been reported recently. Sheth *et al.* reported unilateral superonasal branch retinal and inferior hemiretinal vein occlusion in a 52-year-old male post-COVID-19 patient.[14] No possible etiology was reported neither vasculitic nor nonvasculitic in this case. Staining and leakage in vein walls were reported in FFA referred to phlebitis. Invernizzi *et al.* reported a CRVO case of 54-year-old female with multiple scotoma and flu-like symptoms.[15] Both of these cases were treated with systemic steroid. Sheth *et al.* reported visual improvement and resolution of cystoid macular edema in OCT within a month with 40 mg/day methylprednisolone and intravitreal Ranibizumab (0.5 mg/0.05 mL). In first day, IV methylprednisolone 1 g was administrated for presumed optic neuritis in second case. But after impending CRVO was diagnosed, treatment was converted to oral 60 mg methylprednisolone and it was tapered gradually. Invernizzi *et al*. reported 20/20 visual acuity and complete resolution of retinal findings in multimodal imaging in 1 month with steroid treatment. Walinjkar *et al*. reported a 17-year-old female patient with COVID-19 and CRVO. She responded well to intravitreal Ranibizumab in this report.[16] In our case, systemic steroid therapy was not given in the first presentation in the outer center. The patient had been treated with intravitreal Aflibercept at that time. Systemic corticosteroid had no benefit on visual outcome probably because of late presentation. Despite complete resolution of macular edema and subfoveal fluid, visual improvement couldn't be provided due to accompanying severe macular ischemia.

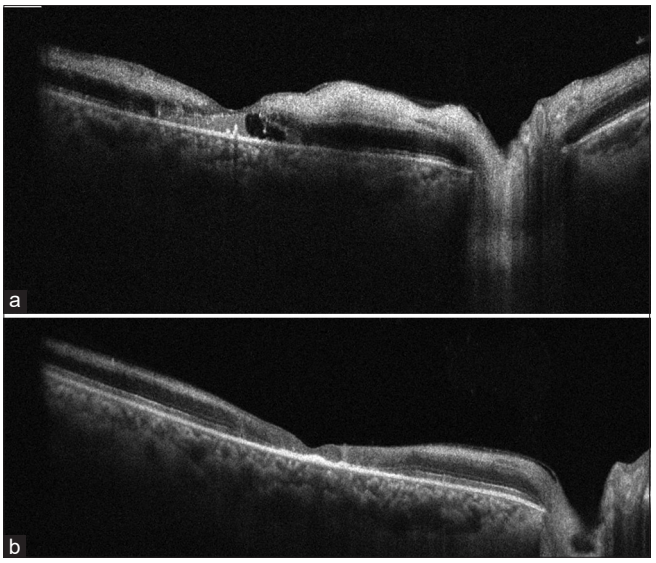


**Figure 3:** Optical coherence tomography before treatment (a) and after systemic steroid treatment (b) After treatment, resolution of macular edema, general thinning at macula, and ellipsoid zone impairment were observed.

Central retinal artery occlusion (CRAO) was also reported in COVID-19 patients.[17,18] Acharya *et al*. reported a 60-year-old male presented with acute vision loss in 12$^{th}$ day of hospitalization.[17] Montesel *et al*. reported CRAO in a 59-year-old African male with severe COVID-19 and overlying bacterial pneumonia.[18] In this case, symptom

onset was after 1 week from discharge. Different from our case, severe pneumonia was present in these cases.

A 37-year-old male COVID-19 patient with vision loss was reported. Vasculitis at lower arcuate and vitritis were noted in this case. Immune response against SARS-CoV-2 was considered as the main pathogenesis.[19] Similar but more severe microvascular impairment was observed in our case and foveal atrophy secondary to prominent ischemia caused poorer visual outcome.

Diffuse retinal whitening and vascular sheathing in large arteries and macular veins indicate a vascular inflammatory involvement. Clinical appearance resembled systemic lupus erythematosus retinopathy. Because of this similarity, immune complexes in microcirculation may be one of the possible mechanisms of COVID-19-related retinal vasculitis. At the inflammatory stage of COVID-19, induced cytokine activity may cause formation of antigen-antibody immune complexes. Complement and IgG deposits in the vessel wall were showed in a patient with Kawasaki disease and COVID-19.[20] Furthermore, association between Kawasaki disease and COVID-19 supports the clinical appearance of immune complex vasculitis in our case.[21]

Time between flu-like symptoms related to COVID-19 and ophthalmologic presentation is seen as approximately 1–3 weeks in different case reports.[14,15] This period was observed as 2 weeks for our case. This period suggests that this phenomenon may possibly be an immune-related disease rather than primary viral vasculitis. Increased cytokine activity after the acute phase of infection seems compatible with this time gap. Immune complex-related diseases are also delayed hypersensitivity reactions.[22] Cytokine storm related increased prothrombotic state probably contributes to this pathogenesis. This theory can be supported with clinical response to systemic steroid in some cases.[14]

In conclusion, COVID-19 patients with visual problems must be considered with care in regard to thrombotic retinal diseases. Early diagnosis and immediate treatment are critical, especially in retinal vascular involvement for better visual prognosis. Larger studies with proper control groups must be performed to ensure the exact role of COVID-19 on retinal vascular diseases.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.


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## Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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