American Journal of Ophthalmology Case Reports 27 (2022) 101669

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Consecutive central and branch retinal vein occlusions in the same eye of a young healthy COVID-19 patient: A unique case report

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ARTICLE INFO

Keywords:
Central retinal vein occlusion
Branch retinal vein occlusion
COVID-19
Macular edema
Anti-vascular endothelial growth factor

ABSTRACT

Purpose: To report a case of consecutive central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) in the same eye correlated with coronavirus disease (COVID-19) of the otherwise healthy patient.

Observations: A 39-year-old woman with the diagnosis of COVID-19 infection for two weeks presented with a nonischemic central retinal vein occlusion (CRVO) in her right eye. The patient was on low-dose aspirin for anticoagulant prophylaxis (100 mg/day) for a week when the CRVO occurred. She had no history of any systemic risk factors for retinal vein occlusion (RVO) and her systemic evaluation failed to identify an etiology for her unilateral CRVO. While she was on monthly follow-up with no additional treatment, she experienced sudden visual acuity decrease in the same eye four months after the first RVO incident and one month after the cessation of aspirin intake. Her best corrected visual acuity (BCVA) was decreased from 20/25+ to 20/63. Her fundoscopic examination revealed increased intraretinal hemorrhages, dilated tortuous veins in the upper hemifield and macular edema. The central macular thickness measurement by optic coherence tomography was increased from 234 μm to 700 μm. The patient refused to undergo a fundus fluorescein angiography. After the diagnosis of the branch retinal vein occlusion with cystoid macular edema was done, the aspirin prophylaxis was restarted, and she received three intravitreal antivascular endothelial growth factor one month apart for her macular edema. Her BCVA improved to 20/20, and macular edema disappeared without any recurrence during the 6-month follow-up.

Conclusions and importance: To the best of our knowledge, this unique case is the first report of consecutive RVOs in the same eye of a healthy young patient associated with COVID-19. As our case report demonstrated, close follow-up and timely initiation of appropriate treatment could give rise to complete resolution of RVO.

1. Introduction

The novel acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19) is known to cause occlusive retinal vascular complication such as central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). Virchow's triad of vessel damage leading to endothelial dysfunction, hypercoagulability, and vascular stasis, plays an essential role in developing retinal vein occlusions (RVOs). Advanced age and systemic vascular disorders such as hypertension (HT), diabetes mellitus (DM), dyslipidemia, coronary artery disease, and hypercoagulability are among the main risk factors for the formation of RVOs. Increased intraorbital or intraocular pressure as in glaucoma are considered as main ocular risk factors in cases with RVO.[1–5]

The patients with COVID-19 infection are at risk of developing RVO due to excessive inflammation and coagulation abnormalities even without systemic predisposition and advanced age.[6,7]

We report a unique case of consecutive CRVO and BRVO in the same eye related to symptomatic COVID-19 infection in an otherwise healthy young adult female patient treated with intravitreal (IV) anti-vascular endothelial growth factor (anti- VEGF) injections. To the best of our knowledge, the presenting case report is the first in the literature in English to demonstrate consecutive CRVO and BRVO in the same eye correlated to symptomatic COVID-19.

2. Case report

A 39- year-old woman with systemic symptoms for fifteen days and diagnosed with COVID-19 infection seven days ago complained of sudden blurred vision in the past 24 hours in her right eye (RE). Her best-corrected visual acuity (BCVA) was 20/25+ in her RE, while it was

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https://doi.org/10.1016/j.ajoc.2022.101669
Received 9 March 2022; Received in revised form 21 June 2022; Accepted 22 July 2022
Available online 31 July 2022

20/20 in her left eye (LE) on Snellen's chart. Intraocular pressure was 18 and 16 mmHg in RE and LE, respectively. Slit-lamp biomicroscopy of the anterior segment was within normal limits; pupils were round, equal, and reactive to direct and indirect light in both eyes. Her dilated funduscopic examination of RE revealed clear vitreous, mild optic disc swelling, few cotton-wool spots located near the optic nerve head, multiple dots, blot, and flame-shaped hemorrhages combined with increased venular tortuosity throughout all four quadrants in the RE (Fig. 1). A spectral-domain optical coherence tomography (Sd-OCT) examination showed a slight diffuse retinal thickening mainly in the nerve fiber layer and absence of macular thickening. Central macular thickness (CMT) was 234 μm in RE. Other Sd-OCT-derived biomarkers of retinal ischemia, including disorganization of the retinal inner layers or paracentral acute middle maculopathy, were not detected. The unaffected LE had a normal posterior segment. A further imaging by the fundus fluorescein angiography (FFA) was planned. But the patient refused to undergo an FFA examination because of its potential risk of allergy and anaphylaxis even she had no known allergy history. The patient was diagnosed with unilateral CRVO in the RE.

The patient had no history of any known risk factors for CRVO. She denied smoking or past use of any systemic drugs or remedies. However, she suffered from flu-like symptoms, sore throat, runny nose, dry cough, minimal dyspnea, fatigue, and high fever for two weeks prior to the ocular symptoms. When she had felt no improvement on health condition, she applied to the local hospital. A real-time reverse transcription-polymerase chain reaction (RT-PCR) from her nasopharyngeal swab was performed seven days after the onset of systemic symptoms. Her RT-PCR test result was positive for COVID-19. She was quarantined without being hospitalized. Only a low-dose aspirin (100 mg/day) as an anticoagulating drug for prophylactic use for three months was prescribed by her family physician.

She was referred to internal medicine and cardiology for further examination after the diagnosis of the unilateral CRVO with no ocular or systemic risk factors. Her comprehensive systemic evaluation, such as blood pressure, complete blood count, serum sugar levels, lipid profile, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, antinuclear antibody, angiotensin-converting enzyme, coagulation tests such as a PTT (Activated partial thromboplastin time), PT (Prothrombin Time), INR (International normalized ratio), hematologic and renal function tests such as blood urea nitrogen, serum creatinine, was unremarkable. Her echocardiography and carotid doppler evaluations were also normal.

A monthly follow-up without any ocular therapy was planned initially. A gradual improvement in retinal findings and a complete resolution of visual symptoms were observed for the first three months. She presented with the complain of a sudden onset of painless vision loss in the same eye on month four. Her BCVA had decreased to 20/63 in the RE. Her funduscopic examination exhibited unilateral increased intraretinal hemorrhages, dilated tortuous veins in the upper hemifield, mainly in the temporal quadrant and the macular edema (Fig. 2). Her Sd-OCT examination demonstrated diffuse thickening of the superior temporal quadrant of the retina, serous macular detachment (SMD), and significant cystoid macular edema (CME) in the RE. The CMT was 700 μm (Fig. 3). She rejected FFA examination again. The diagnosis of BRVO in the RE was done. Her medical history was unremarkable for that period between her first application to our clinic to the last incident. She expressed not receiving vaccination nor experiencing any constitutional symptoms of re-infection of COVID-19 as well. She discontinued aspirin intake for a month. She refused to undergo further hematological re-evaluation, particularly for deficiencies of anticoagulant protein-C, S, antithrombin III, and activated protein-C resistance. The patient was advised to restart daily low-dose aspirin treatment.

Monthly intravitreal bevacizumab (IVB) injection of 2.5 mg/0.1 ml

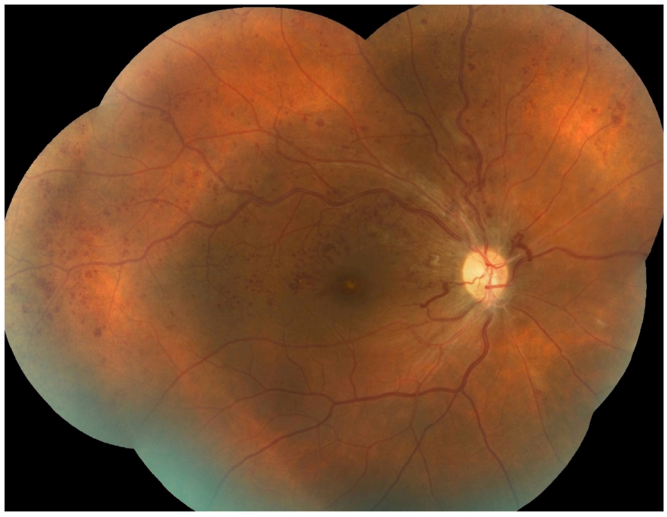

Fig. 2. Wide-field fundus photography exhibits the findings of branch retinal vein occlusion including intraretinal hemorrhages, dilated tortuous veins in the upper hemifield, mainly in the temporal quadrant with the macular edema.

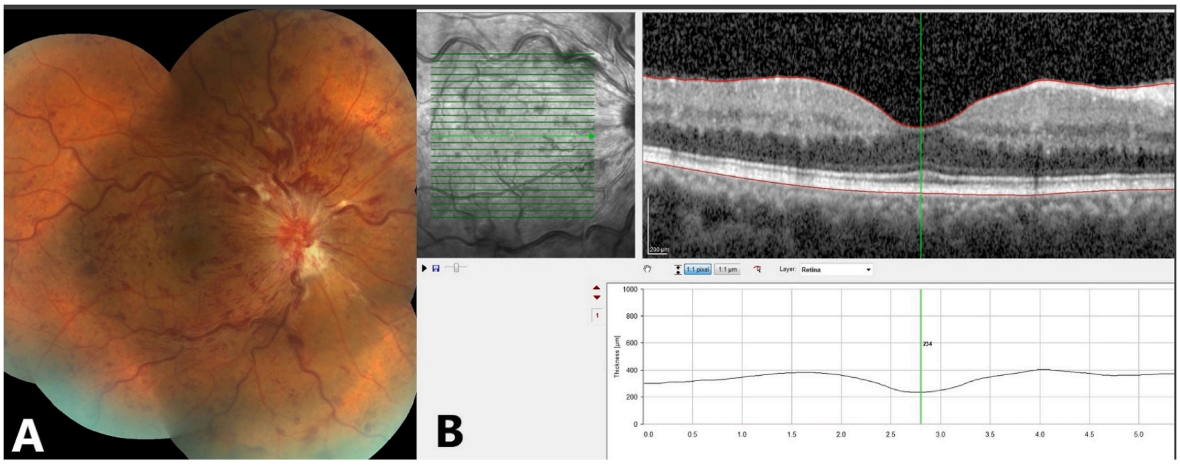

Fig. 1. A- A wide-field fundus photography shows the findings of central retinal vein occlusion (CRVO) including significant disc swelling, cotton-wool spots located near the optic nerve head, and increased venular tortuosity and intraretinal hemorrhages in all four quadrants.
B- An optical coherence tomography (OCT) imaging of CRVO demonstrates slight diffuse retinal thickening on the nerve fiber layer in the absence of macular thickening.

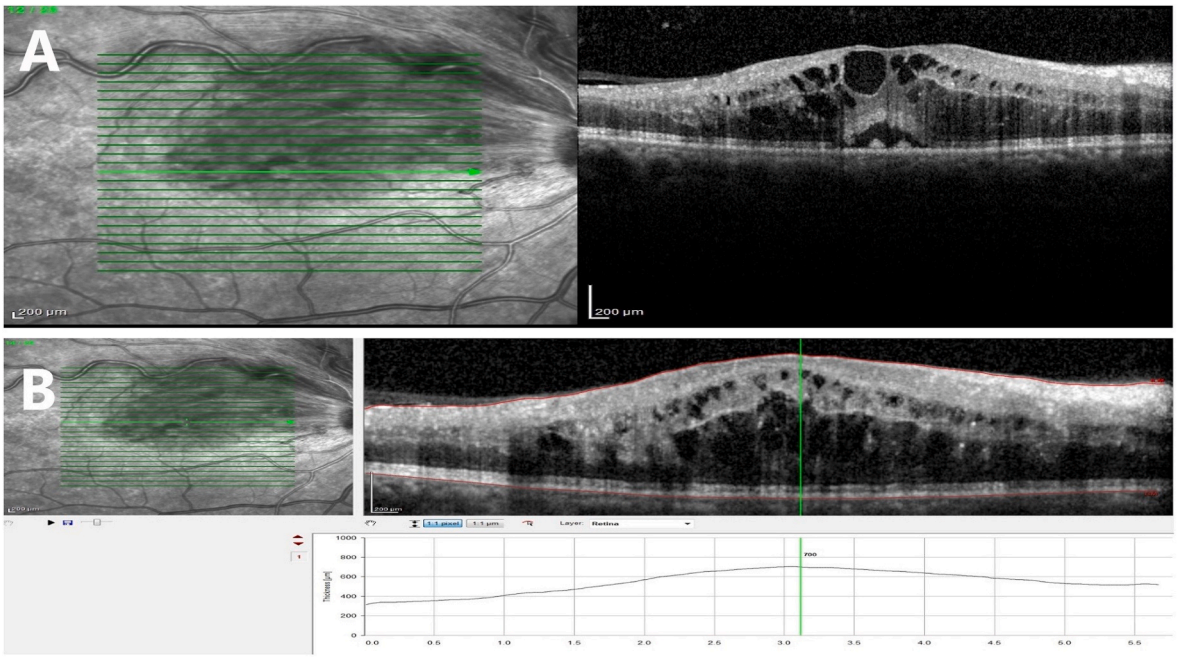

Fig. 3. The optical coherence tomography (OCT) imaging of subsequent branch retinal vein occlusion shows A- Prominent serous macular detachment and B-Cystoid macular edema involving all retinal layers of the foveal region with the central foveal thickness of 700 µm.

was decided. On month one, following the first dose of IVB injection, her BCVA in the RE improved to 20/40, and a prominent resolution of hemorrhages was observed. The CMT decreased to 275µm. After the second dose of IVB injection on month one, BCVA further improved to 20/25. A nearly total resolution of hemorrhages significantly decreased in SMD, and the disappearance of macular edema was observed. The CMT was decreased by 254µ microns. Following the third injection on month three, BCVA was improved to 20/20. The Sd-OCT findings demonstrated complete subsidence of SMD combined with the normal anatomic structure of the macula. The CMT was 249 µm after the last IVB injection (Fig. 4). The patient was continued to monthly follow-up examinations; neither other retinal vascular pathologies nor recurrence of previous diseases were observed during the following six months.

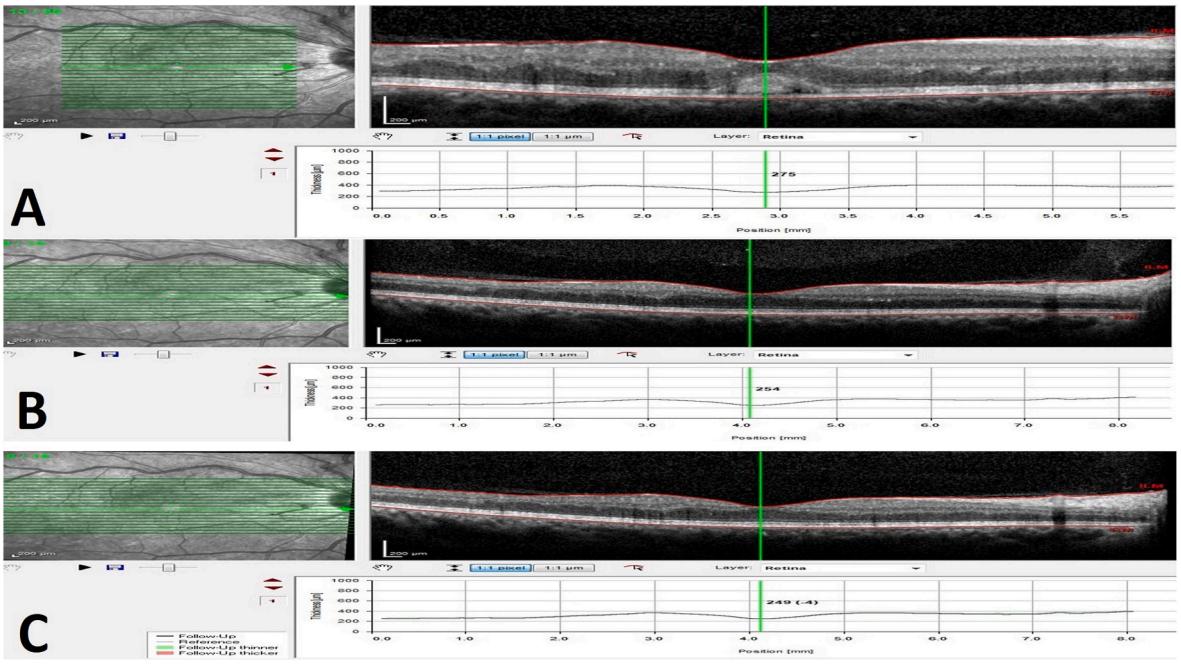

Fig. 4. A series of follow-up optical coherence tomography (OCT) imaging of the macula shows resolution of cystoid macular edema following intravitreal (IV) anti-VEGF injections.A- Decreased serous macular detachment and cystoid macular edema with the central foveal thickness of 275 µm after the first IV anti-VEGF injection.
B- Completely disappeared serous macular detachment with the central foveal thickness of 254 µm after the second IV anti-VEGF injection.
C-Normal anatomic structure of the macula without edema with the central foveal thickness of 249 µm two months after the third IV anti-VEGF injection.

3. Discussion

It has been shown that COVID-19 can cause a high incidence of hypercoagulable state and thrombotic microangiopathy.[2–4] COVID-19 related vision-threatening retinal pathologies, including RVOs, may be irrelevant of any systemic risk factors.[3,4,6] Retinal findings correlated to COVID-19 were initially documented by Marinho et al.[8] Subsequently, several reports have published that the development of either CRVO or BRVO is associated with this viral infection. To the best of our knowledge, the presenting case report is the first in the literature documenting consecutive CRVO and BRVO respectively in the same eye, related to symptomatic COVID-19 infection in the otherwise healthy young subject.

Recently published systematic reviews and case reports have drawn attention to the possible relationship between COVID-19 and RVOs, even in young patients without comorbidities. CRVO generally occurs among patients over 60 years of age. However, most COVID-19 infection related CRVO cases were younger than the usual age of the disease onset, similar to presenting a healthy 39-year-old patient.[3,6,7,9,10] Invernizzi et al.[9] presented the case of a 54-year-old female with CRVO under the treatment of COVID-19 pneumonia. Yahalomi et al. [(10)] reported a healthy 33-year-old patient diagnosed with unilateral CRVO suspected with COVID-19. Walinjkar et al.[2] presented that a 17-year-old girl having CRVO while experiencing symptomatic COVID-19 infection. In Ullah[3] et al.'s systematic review searched from PubMed and Google Scholar during the COVID-19 pandemic, reports 10 cases of CRVO provided specific detailed information on COVID-19. In this literature review, the mean age was 39.3 years, and risk factors such as diabetes mellitus, hypertension, and hyperlipidemia were present in only three patients. They suggested that COVID-19-related hypercoagulability could be a critical risk factor for CRVO irrespective of other well known risk factors.

The incidence of venous thromboembolic events was estimated to be around 25% of the patients with COVID-19 infection even under the prophylactic anticoagulant treatment in intensive care units (ICU). The mechanism for thromboembolic events due to COVID-19 is not precisely explained in the patients with no preexisting comorbidities. It has been postulated that this might be secondary to direct viral infection of the vascular endothelial cells, excessive inflammation, and induction of procoagulant state by hypoxia or immobilization, which could often be seen in ICUs. Klok et al· observed thrombotic complications in 31% of ICU patients with COVID-19.[11] Lodigiani et al. reported thromboembolic complications in 8% of hospitalized patients with COVID-19 despite anticoagulant prophylaxis.[12] According to several reports, PT, a-PTT, and platelet count of the patient with COVID-19-related coagulopathy were found within normal reference intervals.[13,14] Similarly, our patient's blood coagulation test results were within normal limits at the time of the first presentation to our clinic.

Histologic evaluation of autopsy findings of patients with severe COVID-19 has frequently shown diffuse thrombosis in small vessels. It is thought to result from either direct viral infiltration of the endothelial cells or secondary to a delayed immune response to the viral antigen.[6,15,16] Complement-mediated microvascular injury combined with platelet-fibrin microthrombi, which occurs secondary to type-3 hypersensitivity immune-complex disease rather than direct virus invasion, was accounted for the pathology by certain investigators.[6,17,18] It has been shown that retinal vascular involvement generally occurs in 1–4 weeks after the onset of fever in patients with COVID-19. Sheth et al. have observed retinal manifestation ten days after the onset of acute infection.[4] Likewise, the time lag of 14 days between symptoms of COVID-19 infection and CRVO in our patient supports the possibility that a delayed immune complex reaction and deposition could have caused the occlusion of retinal vessels.

In our case, BRVO as another vascular occlusive event developed in the same eye in the fourth month following the onset of CRVO despite the absence of any predisposing factors. Yahalomi et al. reported a 33-year-old male diagnosed with non-ischemic CRVO five weeks after the onset of COVID-19 symptoms.[10] Even their case has one of the longest time intervals between COVID-19 and RVO, the occurrence of BRVO as the second attack of RVO in our patient had a longer period than that of theirs. The appearance of BRVO one month after the cessation of aspirin intake could be evidence of prolonged transient hypercoagulability. Low-dose aspirin prophylaxis has been reported to prevent the formation of new blood clots by reducing hypercoagulability in patients with COVID-19.[3,9,19,20]

RVOs usually reveal visual symptoms caused by macular edema, intraretinal hemorrhage, and ischemia of the retina. Our patient presented us with a slightly decreased vision at the time of the first RVO. She did not have intense cotton wool spots distributed to each four-quadrant as the sign of ischemia. Due to the patient's rejection a FFA was not performed. In Sd-OCT evaluation, no macular edema was detected initially. In month four, a BRVO as a second RVO event in the same eye combined with the prominent cystoid macular edema (CME) was developed. The most accepted therapy for CME secondary to RVOs is the intravitreal injection of either anti-VEGF or steroids. On the grounds of potential risks such as cataract and glaucoma, intravitreal anti-VEGF therapy was preferred to intravitreal steroid injection as first-line therapy in our young patient.

Walinjkar et al. performed three doses of IV anti-VEGF injections in their 17- year-old female patient.[2] In contrast, Sheth et al. preferred a single dose IV anti-VEGF injection combined with oral methylprednisolone (40 mg/day) for the treatment of CME secondary to CRVO in a 52-year-old male patient.[4] Endo et al. preferred IV dexamethasone implantation as first-line therapy for their patient.[21] Although they observed a transient improvement in the fundus findings initially, thereafter, they determined a slight decrease in BCVA and an increase in intraretinal hemorrhages during the follow-up examination. Then, they switched the treatment regimen to a 2.5 mg/0.1 ml dose of IV bevacizumab injection, similar to us.[21] In the study of the case series, Fonollosa et al. reported the baseline CMT as 348.64 ± 83 μm in COVID-19 infection patients with RVOs. The mean CMT was decreased by 273.7 ± 68 μ after the IV treatment either with anti-VEGF, dexamethasone implant or both during 19.6 ± 6 weeks follow-up.[22] Clinical findings and outcomes were similar in our subject to those found in their series. But our case had recurrent RVO in the same eye, and the CMT (700 μ) after the second attack was higher than Fonollosa et al.'s series. However, the CMT decreased to 249 μm after the last injection with no recurrence for six months.

4. Conclusions

As far as we know, this is the first case in the literature developed recurrent RVO in the same eye associated with COVID-19 infection as the young, healthy subject without any known risk factors. In addition, to the best of our knowledge, it was the most prolonged time interval between the recovery of COVID-19 and the second RVO attack in a patient. As our case report demonstrated, close follow-up and timely initiation of appropriate treatment could give rise to complete recuperation. Further investigation is recommended to better understand the correlation between recurrence of RVO along with them effectively and optimum duration of aspirin prophylaxis in patients with COVID-19 infection.

Funding

No funding or grant support.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Patient consent

This report does not contain any personally identifying information.

Declaration of competing interest

The following authors have no financial disclosures: AGA, None; EE, None.

Acknowledgments

None.

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