**Retinal vein occlusion in COVID-19: A novel entity**

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Coronavirus disease 2019 (COVID-19) is a form of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has been declared a pandemic by the World Health Organization (WHO). Ocular manifestations related to COVID-19 are uncommon with conjunctivitis being reported in a few cases. We report a unique case of vasculitic retinal vein occlusion (RVO) secondary to COVID-19 in a 52-year-old patient who presented with the diminution of vision in the left eye 10 days after he tested positive for SARS-CoV-2. All investigations for vasculitis were negative. This case supports the mechanism of thrombo-inflammatory state secondary to the “cytokine-storm” as the pathogenesis for systemic manifestations of COVID-19.

**Key words:** COVID-19, retinal vein occlusion, SARS-CoV-2, vasculitis

Coronavirus disease 2019 (COVID-19), which began in China in December 2019, has now spread globally and has been described as a pandemic by the World Health Organization (WHO). Among ocular manifestations, conjunctivitis has principally been reported. We hereby report a novel ocular complication of COVID-19 in the form of vasculitic retinal vein occlusion (RVO).

**Case Report**

A 52-year-old male presented to the vitreoretinal services with decreased vision in the left eye (OS) since day 1. He gave a history of fever 10 days ago for which he underwent reverse transcriptase polymerase chain reaction analysis of sputum samples and was diagnosed positive for COVID-19. On contact-tracing, no primary source of infection was found, and he was quarantined and treated in hospital for 1 week and discharged in stable condition. At presentation, his best-corrected visual acuity (BCVA) in OS was 6/60 while it was 6/6 in the right eye (OD). On fundus examination, the patient had OS inferior hemiretinal vein occlusion with superonasal branch retinal vein occlusion and macular edema [Fig. 1]. Fundus fluorescein angiography (FFA) of OS revealed dilated and tortuous retinal veins in inferior and superonasal quadrants which showed significant vessel wall staining and leakage in late phases suggestive of extensive phlebitis (Blue-arrow; Fig. 2). There was no evidence of arteritis or perivasculat sparing. Areas of hypofluorescence were noted in involved areas that clinically corresponded to hemorrhages, suggestive of blocked fluorescence (Yellow-arrow; Fig. 2). Additional areas of hypofluorescence were also noted in peripheral regions of affected quadrants suggestive of capillary non-perfusion (CNP) (Yellow-arrow; Fig. 2). Dye leakage at the macula and optic disc was also observed. Spectral-domain optical coherence tomography (SD-OCT) of OS showed the presence of serous macular detachment (SMD; Orange-arrow; Fig. 3a) and significant cystoid macular edema (CME), with cysts present in the outer nuclear layer (ONL; Blue-arrow; Fig. 3a), inner nuclear layer (INL; Red-arrow; Fig. 3a), and ganglion cell layer (GCL; Green-arrow; Fig. 3a) [Fig. 1b]. Additionally, the presence of disorganization of retinal inner layers (DRIL) was also seen (Yellow-arrow; Fig. 3a).

Systemic workup for vasculitic and non-vasculitic causes of RVO, including blood pressure, complete blood count, erythrocyte sedimentation rate, serum lipid profile, sugar levels, plasma protein electrophoresis, C-reactive protein, serum homocysteine level, serum angiotensin-converting enzyme (ACE), tuberculin skin testing, interferon-gamma release assays for Mycobacterium (QuantiFERON-TB Gold), high-resolution computerized tomography scan, thrombophilia-screening, and autoantibodies was unremarkable. The patient was diagnosed with vasculitic RVO secondary to COVID-19 and treated with oral methylprednisolone (40 mg/day) and intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection of the ranibizumab biosimilar, Razumab® (Intas Pharmaceuticals, Ahmedabad, India; 0.5 mg/0.05 mL). At the end of 1 month, his BCVA improved to 6/9. On SD-OCT, there was complete resolution of SMD and CME [Fig. 3b], resolving DRIL (ELM; Yellow arrow; Fig. 3b), presence of subfoveal loss of ellipsoid zone (EZ) and external limiting membrane (ELM; red arrow; Fig. 3b), and small intraretinal hemorrhages seen as intraretinal hyperreflective lesions (ELM; Blue arrow; Fig. 3b).

**Discussion**

The “2019 novel coronavirus” (2019-nCoV) is an enveloped, non-segmented positive-sense RNA virus belonging to the beta-Coronaviridae family. It is associated with atypical pneumonia and acute respiratory distress syndrome with notable mortality rates. This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

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Figure 1: Color fundus photograph (CFP) of the left eye demonstrating inferior hemiretinal vein occlusion (HRVO) with superonasal branch retinal vein occlusion (BRVO)

Figure 2: Fundus fluorescein angiogram (FFA) of the left eye showing the presence of dilated tortuous vein in inferior and superonasal quadrants with late phases showing considerable staining and leakage from the vessel walls (Blue arrow). Multiple areas of hypofluorescence are seen which correspond to retinal hemorrhages clinically, suggestive of blocked fluorescence (Yellow arrow). Furthermore, the involved quadrants also illustrated additional areas of hypofluorescence suggestive of capillary non-perfusion (CNP; Blue arrow). The macular region and optic disc also showed hyperfluorescence in late phases suggestive of leakage.

Figure 3: (a) Spectral-domain optical coherence tomography (SD-OCT) of the left eye at baseline illustrating the presence of serous macular detachment (Orange arrow; a), cystoid macular edema (cysts located in outer-nuclear-layer (ONL; Blue arrow; a), inner-nuclear-layer (INL; Red arrow; a) and ganglion-cell-layer (GCL; Green arrow; a) and disorganization of retinal-inner-layers (DRIL; Yellow arrow; a). (b) Follow-up SD-OCT at one-month showing complete resolution of SMD and CME, resolving DRIL (Yellow-arrow; b), subfoveal loss of ellipsoid-zone (EZ) and external limiting membrane (ELM; Red arrow; b), and small intraretinal hyperreflective lesions suggestive of intraretinal hemorrhages (ELM; Blue arrow; b)

Ocular manifestations have also been associated with COVID-19, most common being conjunctivitis seen in 0.8% of patients. Marinho et al. have described retinal findings which include subtle cotton wool spots and microhemorrhages associated with COVID-19. Subsequently, there have been a few publications that have expressed concern regarding the interpretation of these fundus and OCT findings. They have suggested further imaging in the form of infrared reflectance as the OCT findings and locations of the purported lesions corresponded to retinal vessels, longer follow-up of the supposed cotton wool spots as they could be confused with myelinated nerve fibers, and additional details regarding comorbid conditions present in those patients such as diabetes which can itself give rise to these retinal findings.

In the current case, the patient was a young adult with fresh RVO. In such a clinical scenario and in the absence of any comorbidities such as diabetes, hypertension, or tuberculosis, the common pathogenesis more often than not is vasculitis. With the principal part of vasculitic etiologies for RVO ruled out by investigations, and with an underlying critical ailment in the form of COVID-19, we made a presumptive diagnosis as vasculitic-RVO secondary to COVID-19. Moreover, systemic vasculitis has been extensively described in relation to COVID-19. Histologic evaluation of biopsy samples has frequently shown the involvement of the lung, liver, kidney, and skin. This occurs secondary to type-3 hypersensitivity (immune-complex disease) wherein the deposition of immune-complexes leads to a pro-inflammatory stage and triggers a “cytokine-storm.” In the present case,
the retinal vasculitis was the only systemic manifestation which the patient suffered from. This is an interesting finding because any patient with retinal vasculitis without any known risk factors and keeping the current pandemic of COVID-19 in mind should be recommended an evaluation for 2019-nCoV.

The primary cellular receptor for the entry of SARS-CoV-2 is the angiotensin-converting enzyme-2 (ACE2), which has been detected in the aqueous humor and the retina in humans.[1] Casagrande et al. evaluated retinal biopsy samples of 14 eyes of COVID-19 patients and demonstrated viral-RNA of SARS-CoV-2 in three of them.[2] Based on literature and current knowledge about the disease and its pathogenesis, the retinal vasculitis in our case could be either because of the thromboinflammatory cascade secondary to the “cytokine-storm” immune response or because of direct involvement of viral particles. Similar occlusive retinal vasculitis has also been described in other viral infections such as dengue and chikungunya.[7,8] Additionally, other posterior segment involvements in these conditions include foveolitis, retinitis, neuroretinitis, optic neuritis, and panuveitis. The proposed mechanisms for such ocular manifestations in these viral entities also include direct viral involvement or a delayed immune response to the viral antigen.[7,8] Considering that posterior segmental involvement is usually seen in 1–4 weeks following the onset of fever in these diseases, many authors favor immune-mediated pathogenesis as compared to direct virus infection.[8,9] Likewise, even in our case, the time lag of 10 days between acute infection and retinal manifestation suggests a delayed immune complex deposition causing occlusion of retinal vessels. This could be a part of systemic vasculitis associated with COVID-19, which is commonly seen 7 days after the onset of fever. In view of these inflammatory organ injuries precipitating thromboembolism, recent studies have recommended the use of glucocorticoids such as dexamethasone and anticoagulants such as heparin for better prognosis and reducing mortality.[6,10] Our patient too was started on oral steroids to surmount the potential systemic inflammation.

**Conclusion**

With the prevailing information regarding the ocular manifestations, much is still unknown regarding the virus and its effects. We believe that our case report whereby for the first time in literature, we illustrate vasculitic-RVO secondary to COVID-19, will allow us to increase our knowledge about the various ocular manifestations and be vigilant about this vision-threatening ocular disease.

**Declaration of patient consent**

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

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**Conflicts of interest**

There are no conflicts of interest.

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