Hemi-central retinal vein occlusion as a rare manifestation of the hypercoagulable state in COVID-19

Jose R Russe-Russe ,[1] Alejandro Alvarez-Betancourt,[1] Amanda Milburn,[2] Prachi Anand[3]

[1]Internal Medicine, Nassau University Medical Center, East Meadow, New York, USA
[2]College of Osteopathic Medicine, NYIT, Old Westbury, New York, USA
[3]Internal Medicine/Rheumatology, Nassau University Medical Center, East Meadow, New York, USA

Correspondence to
Dr Jose R Russe-Russe; joseramonrusserusse@gmail.com

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SUMMARY

To date, COVID-19 has no definite effective targeted therapy, and management is primarily supportive. Central retinal vein occlusion (CRVO) is frequently caused by systemic risk factors posing hypercoagulable states. In April 2020, a female patient with a history of hypertension, diabetes mellitus and chronic kidney disease presented with 2 days of loose, watery stools, nasal congestion and severe lethargy. The patient denied dyspnoea or fever. A week after the initial symptoms, the patient reported decreased vision from the left eye. Dilated funduscopy and fluorescein angiography suggested hemi-CRVO. The patient refused intravitreal antivascular endothelial growth factor agents because of non-severe visual loss. Testing was positive for COVID-19 IgG antibodies; reverse transcription PCR was not available. Vision improved within 3 weeks of presentation. We recommend that clinicians keep a high suspicion for acute onset of thrombotic events in patients with COVID-19 and thrombotic predisposing risk factors.

BACKGROUND

COVID-19, a form of SARS-CoV-2, has perplexed the medical community given its wide reach on the susceptible population and ever-growing evidence of its systemic involvement. Recent medical interest has revolved around preventing complications derived from a well-described hypercoagulable state. International Society on Thrombosis and Haemostasis, the American Society of Hematology and the American College of Cardiology have formally issued recommendations regarding prophylactic and therapeutic anticoagulation. Retinal vein occlusion has a prevalence of 0.1%–0.5% in the elderly population.[1 2] This occlusion is classified according to the structural level vein that is occluded.[1] The central retinal vein occlusion (CRVO) occurs at the level of the lamina cribrosa or posterior to it and can be classified as ischaemic and non-ischaemic subtypes.[1 2] In eyes with two central retinal veins, the superior vein drains the upper half of the retina, and the inferior vein drains the lower half, and the occlusion of one of these veins is known as hemi-CRVO.[3] This type of occlusion consists of either venous stasis due to CRVO without significantly associated ischaemia and haemorrhagic retinopathy due to CRVO associated with ischaemia.[3] CRVO is most frequently caused by systemic risk factors posing hypercoagulable states.[4] These risk factors include hypertension, as the most significant risk factor, followed by complicated diabetes mellitus with renal disease or neuropathy, and to lesser extent hyperlipidaemia which duration and severity influence the atherosclerotic changes in the retinal vessels.[4] We report a rare case of hemi-CRVO as a complication from COVID-19 hypercoagulability.

CASE PRESENTATION

In April 2020, a female patient with a known medical history of hypertension, diabetes mellitus type 2 and chronic kidney disease stage 4 presented with 2 days of constitutional symptoms non-specific for COVID-19 such as loose, watery stools, nasal congestion and severe lethargy. The patient denied shortness of breath or fever. No molecular testing was available at the time. The patient was afebrile and not found to be hypoxic throughout the whole course of her illness. About 7 days after the initial symptoms, the patient reported decreased visual acuity from the left eye, and her right eye was at baseline. On objective examination, pupils were equal, round and reactive to light, and intraocular pressures were within normal limits in both eyes. An ophthalmologic investigation including dilated funduscopy and fluorescein angiography, figures 1 and 2, showed hemi-CRVO. Therefore, findings concluded that the patient would benefit from intravitreal antivascular endothelial growth factor (anti-VEGF) agents. Still, the patient refused conventional therapy because she had a non-severe visual loss.

INVESTIGATIONS

Dilated funduscopy, figure 1, showed superior hemi-CRVO, macular oedema (MO), exudates and cotton–wool spots. Fluorescein angiography, figure 2, showed superior hemi-CRVO, collateral vessels, capillary telangiectasia and microaneurysms. The patient did not undergo testing for D-dimers, platelet count, interleukin-6, C reactive protein or other acute inflammatory markers. The patient decided to stay home and did not have access to these tests. Antibody testing performed 4 weeks after the onset of symptoms was positive for COVID-19 IgG antibodies. At that time, April 2020, COVID-19 reverse transcription PCR testing was not readily available as standardised testing.

DIFFERENTIAL DIAGNOSIS

In the differential diagnoses of CRVO, hyperviscosity retinopathy and ocular ischaemic syndrome

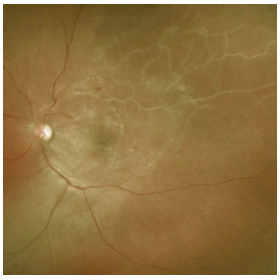

Figure 1 Dilated funduscopy showing superior hemi-central retinal vein occlusion, macular oedema, exudates and cotton–wool spots.

are the two most important to rule out. Hyperviscosity retinopathy may mimic CRVO; these include conditions that affect the blood vessel walls, blood-clotting mechanisms or blood viscosity.[5] Other ocular manifestations have also been associated with COVID-19, conjunctivitis being the most commonly reported, seen in 0.8% of patients.[5 6] Although the patient had no prior history of these diseases, the final diagnosis of hemi-CRVO was reached after the diagnostic ophthalmologic examinations were performed.

TREATMENT

Following the results of the ophthalmologic examination, it was concluded that the patient would benefit from intravitreal anti-VEGF drugs. However, the patient refused any treatment as she was worried about intravitreal injections and relied on the spontaneous resolution of her symptoms as she had a non-severe visual loss. Anticoagulation was not considered as in April 2020; therapeutics for COVID-19 were not precise. The patient was not vaccinated with the COVID-19 vaccine before presentation due to vaccination not being available at the time.

OUTCOME AND FOLLOW-UP

The patient preferred to stay home. She reported visual acuity improvement at 3 weeks from the presentation and was scheduled for follow-up with ophthalmology in one to 1–3 months. The patient continues to follow-up with her ophthalmologist every six to 6–8 weeks. To date, there has been no recurrence of CRVO after a year of initial presentation. The patient is currently vaccinated with the COVID-19 vaccine and has had an unremarkable course to date.

DISCUSSION

Anatomically, the two-trunked central retinal vein is a congenital abnormality where two or more retinal venous trunks enter the optic disc and pierce the lamina cribrosa as independent vessels.[3] When an occlusion occurs to one of these segments, it is known as hemi-CRVO. Its pathogenesis is similar to CRVO, presenting either venous stasis or haemorrhagic retinopathy.[3] Coincidentally, this case presented a patient with hemi-CRVO likely due to venous stasis secondary to increased hypercoagulability, making it more benign and self-limiting than, as compared with its counterpart, haemorrhagic retinopathy, more malignant. Furthermore, a study investigating the natural history of visual outcome of 65 patients with hemi-CRVO suggested a good prognosis within 3 months of presentation.[7]

The pathogenesis of CRVO is multifactorial, but it is well known that arteriolosclerosis and Virchow's triad, that is, endothelial injury, hypercoagulability and abnormal blood flow, are well known strong contributors to thrombotic events leading to vein occlusions.[8] Furthermore, damaged endothelium producing low-grade inflammation, upregulation of inflammatory mediators that disrupt the blood–retina barrier and decreased delivery of oxygen to the retina are essential factors that directly affect the retinal microvasculature and are involved in the pathogenesis of CRVO.[8] MO is caused by the leakage of proteins, lipids and blood into the retina when there is increased vascular permeability due to disruption of the blood–retina barrier, as a result of VEGF, as seen in figure 1. Thus, MO may be the main contributor to vision loss in CRVO. Still, the correlation is reduced at the acute and chronic stages due to confounders such as macular ischaemia, atrophy and haemorrhages in hemi-CRVO.[9] Collateral vessels in CRVO are considered chronic, figure 2, especially in patients with systemic diseases such as diabetes mellitus, hypertension and hyperlipidaemia, may affect the resolution of MO.[8] Microaneurysms, figure 2, may occur in systemic and retinal diseases, including ischaemic, infectious, inflammatory and haematologic conditions, as vital signs of progression of systemic disorders in older age.[8] Anti-VEG therapy is considered first-line therapy and provides rapid resolution of MO and vision improvement.[8] However, high cost, high recurrence rate and the need for frequent visits and injections pose a limitation of this therapy.[8]

Ocular manifestations have been associated with COVID-19, conjunctivitis being the most commonly reported, seen in 0.8% of patients.[6] These manifestations are likely attributable to the fact that the primary cellular receptor for the entry of SARS-CoV-2 is the ACE2, which has been detected in the human aqueous humour and retina.[10 11] Thus, this pathophysiology exemplifies a proposed mechanism by which COVID-19 could directly affect retinal endothelial cells and accelerate those with predisposing risk factors. In addition, Wu *et al* noted that patients positive for SARS-CoV-2 with ocular symptoms had higher white blood cell and neutrophil counts, C reactive protein and higher levels of procalcitonin and lactate dehydrogenase compared with patients without ocular abnormalities.[10 12]

A retrospective study that analysed the prevalence of COVID-19 among CRVO patients described that 33.3% suffered from left CRVO compared with 66.7% with right CRVO.[13] Furthermore, the same study found that 70% of these patients had hypertension, 50% had hyperlipidaemia and 28.8% had diabetes mellitus, where 31.8% had two of these risk factors and 13.6% had all three contributing even further to deleterious hypercoagulability.[13]

COVID-19 has posed a challenge to healthcare systems and professionals given its evolving reach as respiratory disease and a deleterious systemic disease. By now, it has been well described that COVID-19 causes a hypercoagulable state, which manifests primarily as venous thrombotic events. Furthermore, different case series and retrospective analyses have reported the incidence

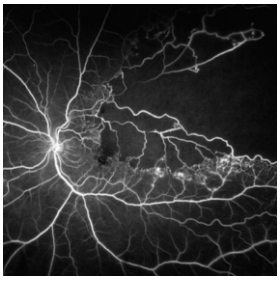

Figure 2 Fluorescein angiography showing superior hemi-central retinal vein occlusion, collateral vessels, capillary telangiectasia and microaneurysms.

of pulmonary embolism, venous thromboembolism, stroke and critical limb ischaemia in patients with COVID-19.[14–18]

Several randomised clinical trials have been undergone for the treatment of retinal vein occlusions. Between them, the Standard Care vs Corticosteroid for Retinal Vein Occlusion study and the Geneva study concluded that anti-VEGF agents were superior to steroids because of the more favourable side effect profile and better visual acuity results in patients with CRVO.[19] In addition, surgical treatments studied include radial optic neurotomy, surgical formation, vitrectomy, arteriovenous sheathotomy, tissue plasminogen activator and anticoagulation with antithrombotic or thrombolytic medications. Still, no strict scrutiny in randomised clinical trials has made them superior to anti-VEGF agents.[19] Therefore, current guidelines recommend anti-VEGF agents as the treatment of choice for retinal venous occlusive disease, including hemi-CRVO and CRVO.[19]

Among the constellation of complications associated with venous thrombosis, this patient meets the criteria for classic risk factors for retinal vein occlusion, including diabetes mellitus type 2, hypertension and, as a nuance, a hypercoagulable state secondary to COVID-19 infection. Therefore, we recommend that clinicians keep a high suspicion for acute onset of thrombotic events in patients with COVID-19 and thrombotic predisposing risk factors.

Learning points

- This case adds to the existing literature that demonstrates a synergistic effect of preexisting central retinal vein occlusion (CRVO) risk factors and infection with COVID-19 for worsening hypercoagulability.
- Patients with COVID-19 are at risk for vascular occlusive events, and early detection and treatment are paramount in optimising health.
- In the setting of patients positive for COVID-19, providers must be vigilant about systemic manifestations and in addition, vision-threatening ocular diseases such as CRVO.
- Reiterates the need for protocols for ophthalmologists given that patients presenting with CRVO can have a possible underlying, undiagnosed, active or previous COVID-19 pathology.

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ORCID iD

Jose R Russe-Russe http://orcid.org/0000-0001-7801-2165

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