Retinal complications following COVID-19: Real-life insights and implications

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Case Report

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Abstract

Purpose: This case series investigated and elucidated various retinal pathologies observed in patients with COVID-19 infection. We sought to understand the prevalence and manifestations of these conditions by exploring the link between COVID-19 and retinal pathologies.

Methods: We conducted a retrospective analysis of patients diagnosed with COVID-19 who subsequently exhibited retinal pathologies. Medical records and ophthalmic imaging data were thoroughly reviewed to identify specific cases of central serous chorioretinopathy (CSCR), paracentral acute middle maculopathy (PAMM), bilateral Krill’s disease, and vessel occlusion.

Results: Our analysis revealed a spectrum of retinal pathologies in patients with COVID-19 infection. These included CSCR, PAMM, bilateral Krill’s disease, and central retinal artery occlusion. These pathologies appear to be closely associated with the inflammatory and thrombotic effects of the virus on the retina.

Conclusion: This case series demonstrates the importance of recognising and promptly managing retinal pathologies in individuals recovering from COVID-19 to mitigate vision loss. Although our findings suggest a strong connection between these ophthalmic manifestations and COVID-19 infection, further research is warranted to establish a definitive correlation and expand our understanding of these conditions in the context of post-COVID-19 recovery.

Key messages

- Retinal pathologies have been observed in patients following COVID-19 infection.
- This study revealed a spectrum of retinal pathologies associated with COVID-19, including central serous chorioretinopathy (CSCR), paracentral acute middle maculopathy (PAMM), bilateral Krill’s disease, and vessel occlusion.
- Prompt recognition and management of these retinal pathologies in COVID-19-recovering individuals are crucial for mitigating vision loss.

Introduction

In December 2019, the highly transmissible Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus spread rapidly. The pandemic caused unprecedented disruptions to routine medical care, affecting patients globally. Early research suggested that COVID-19 ocular symptoms were uncommon. From December 2019 to January 2020, only 9 (0.8%) of 1,099 patients from 552 hospitals in 30 provinces of China were reported to have "conjunctival congestion" [1]. In a meta-analysis conducted in 2021, Nasiri et al. found that conjunctivitis was the most common ocular condition among 7,300 COVID-19 patients (≈ 89%), with a prevalence of all ocular manifestations of ≈ 12% [1]. However, following or during infection, patients also demonstrated changes to their posterior eye segments, which are the
subjects of these case studies. Further information about the connections of connections to retinovascular illnesses is continually being reported [2–4]. With a rise in newer and potentially more threatening variants of the COVID-19 virus, being acquainted with the possible clinical manifestations would pave the way for an effective treatment plan and improve patient clinical outcomes and visual acuity.

**SARS-CoV-2 pathophysiological and ophthalmological correlates**

According to preliminary clinical data, ophthalmologic COVID-19 cases can usually be characterised by an associated inflammatory state, vasculopathy, thrombotic microangiopathy, and intravascular coagulopathy [4].

Either indirectly through secondary thrombotic insults or directly via tissue damage, SARS-CoV-2 and its immunogenicity affect the retina [5]. The advancement of multimodal imaging studies, including SD-OCT angiography, fundus fluorescein angiography (FFA), fundus autofluorescence (FAF), and Clarus fundus imaging, has allowed physicians to make accurate diagnoses of either primary or secondary retinal abnormalities, mostly connected to intraretinal vascular structures.

The following is a collection of clinical cases highlighting COVID-19-related retinal pathologies. The patient cohort was assessed at Svjetlost Eye Clinic in Zagreb, Croatia. The patients presented had visual symptoms during COVID-19 infection and were observed immediately after the infection (min. <2 weeks post-diagnosis). The associated COVID-19 vaccination was not assessed in this study. Future work, especially with the threat of exposure to a diverse set of COVID variants, should focus on the benefit of vaccination in minimising ophthalmologic symptoms.

**Case 1: CSCR**

The clinical significance of CSCR belongs to the *Pachychoroid Spectrum*, which refers to a group of clinical entities that characteristically demonstrate the presence of a thickened choroid formed via similar pathophysiological mechanisms [6]. Characteristic presenting symptoms include metamorphopsia, blurred vision, micropsia, and relative scotoma. Typical OCT findings include a pachychoroid, RPE detachment, and subretinal fluid, whereas a *speckled* hyper-autofluorescence appearance is visible on FAF. Findings typically resolve within 6 months, and if not, CSCR is referred to as *chronic* [7]. The initial treatment of choice is observation as CSCR usually resolves spontaneously or with the addition of local nonsteroidal anti-inflammatory (NSAIDs) drops or carbonic anhydrase inhibitors. Eplerenone, micropulse laser, and end-point laser, along with half a dosage of photodynamic therapy, are appropriate treatment options for patients with chronic CSCR, at which point vision loss of some degree has occurred [8].

Our case includes a 43-year-old male presenting with decreased visual acuity in his right eye manifesting 2 weeks after testing positive for COVID-19, as confirmed by polymerase chain reaction (PCR). He presented with no comorbidities or prior ophthalmologic complaints. He had a mild case of COVID-19 and...
was not treated with corticosteroids. SD-OCT confirmed the presence of parafoveal neurosensory detachment with subretinal fluid as observed in Fig. 1. The patient was diagnosed with CSCR and prescribed bromfenac (NSAID) drops twice daily. At the 3-week follow-up examination, all previous diagnostic findings showed signs of improvement, and baseline visual acuity (VA) of 20/20 was restored.

Case 2: Paracentral Acute Middle Maculopathy

COVID-19 has also been linked to PAMM, which is characterised by hyper-reflective alterations at the level of the outer plexiform (OPL) and inner nuclear retinal layers (INL) and involves ischaemia of the deep retinal capillary plexus [9]. Approximately 47.5% of cases of PAMM and AMN have been documented after viral infection [10]. Only 2 studies have attempted to associate PAMM manifestation with COVID-19 infection, one of which described it as a post-infectious complication, whereas the other described AMN related to COVID-19 infection in conjunction with acute myeloid leukaemia [10, 11].

Our case documents a 51-year-old male patient who complained of visual field defects in his right eye. Symptoms appeared immediately after overcoming COVID-19 infection, as verified by PCR. The patient was diagnosed with type II diabetes mellitus and hypertension. Whitish lesions were found parafoveally and along the inferior arcade on DFE. Peripapillary and dot-blot haemorrhages in all 4 quadrants along with ischaemic zones were evident bilaterally, as can be seen in Fig. 2A. SD-OCT showed bilateral placoid lesions in the inner retinal layers in both eyes, predominantly in OD, visible in Fig. 2B. BCVA was 18/20 in OD and 20/20 in OS. The patient was prescribed aspirin (100 mg preventatively) and was urgently referred for complete systemic analysis and scheduled for a coagulogram, with a specific indication for D-dimer level analysis.

Case 3: Bilateral Krill’s Disease

Krill’s Disease is an eye condition that affects healthy adults aged 20–50 years, with no gender or racial predilection. Symptoms of bilateral Krill’s disease include blurred or distorted vision, dark spots or floaters in the vision, and changes in colour vision [13]. Usually, only one eye is affected; however, bilateral involvement may occasionally occur. DFE characteristically shows fine pigment stippling in the macula surrounded by a hypopigmented halo. Early phases of the disease may show upward displacement of the ELM and mild transient thickening of the RPE/Bruch's complex, whereas FAF shows hyperfluorescence at the fovea due to a transmission window defect [14]. Typically, no treatment is necessary because of the self-limiting nature of the disease, and outcomes usually involve complete VA restoration. Spontaneous resolution of lesions and recovery of vision occurs in all patients without treatment, which may include medications that target abnormal blood vessels, laser therapy to seal leaking blood vessels, or surgery to remove abnormal blood vessels or scar tissue. Poor prognostic factors include a poor baseline VA of 20/70 and extensive retinal involvement involving the ONL. Recurrences are exceedingly rare.

Our case included a 41-year-old male patient who reported seeing a "luminous crescent" in the visual field of his right eye for 3 days. The patient initially complained of blurred vision lasting one month, which
began one week after he was diagnosed with COVID-19. BCVA OD was 18/20, whereas OS was 20/20. On DFE, OD, and OS, yellowish punctate lesions were observed in the macula and inferior to the lower temporal arcade. FAF of both eyes also showed hyperfluorescent and hypofluorescent spots in the macular area and around the arcades, evident in Fig. 3A. SD-OCT of both eyes (Fig. 3B) showed RPE attenuation and choroidal thickening with small intraretinal hyperreflectivity. At the 3-week follow-up, OCT and FAF scans were near normal, and the VA had recovered.

Case 4: central retinal artery occlusion

Patients lacking the typical systemic vascular risk factors have been documented to experience central retinal vein and artery occlusions after being diagnosed with COVID-19. The virus’s prothrombic and inflammatory potential, which causes endothelium damage and microangiopathic injury, is part of the proposed disease process [15–17].

Our case included a 40-year-old patient who presented with a lower visual field defect one week after he was infected with COVID-19. Fundus examination revealed occlusion of the inferior rami of the central retinal artery, which was visualized as thinning on SD-OCT (Fig. 4).

Discussion

Although a larger set of clinical studies is needed to establish a definite correlation between ophthalmic pathologies manifesting post-COVID infection, some theories have been proposed. First, an enhanced thromboembolic condition can also be caused by immune cells and complement debris [5]. Second, the ACE-2 receptor, which is abundant in the retina, serves as the cognate receptor of the viral spike protein, indicating tissue tropism of SARS-CoV-2 in the retina [18]. Similarly, TMPRSS2, which is characteristic of cells comprising the posterior eye segment, undergoes cleavage, permitting the effective cellular entrance of the virus [19]. After access is achieved, a virulent cascade is initiated by cytokine-driven systemic inflammation and vascular leakage.

Additionally, published studies have offered theories supporting the "stress state" imparted by COVID-19 [20, 21]. Upon ACE-2 receptor binding, SARS-CoV-2 attaches to host cells. When ACE-2 receptors are expressed, endothelial cells become susceptible to the virus, resulting in systemic endothelial dysfunction. The density of ACE-2 receptors is higher in all major organs, including the lungs, heart, veins, and arteries. Vasoconstriction, ischaemia tissue oedema, and procoagulant conditions are all side effects of endothelial dysfunction, including endothelitis [22, 23]. ACE-2 receptors are also heavily expressed along the choroidal vasculature and are activated upon cortisol binding. This can lead to many posterior segment complications, such as increased CSCR permeability or ischaemic complications of PAMM, the endothelitis of Krill’s disease, or prothrombotic complications, such as retinal vessel occlusion [11, 17].

CSCR is also a known complication of steroid administration, irrespective of the drug dose or administration route [8]. It can occur for a few days to months after drug initiation. Steroids
(intravenously, orally, or inhaled) are commonly used in the management of patients with COVID-19, and all previous reports of post-COVID-19-associated CSCR had a history of taking steroids. Therefore, the most probable aetiology of post-COVID-19-associated CSCR may be steroid use. However, in our patient, steroids were not used in COVID treatment.

PAMM and AMN are well-known complications of the posterior segment after viral infection. J. Virgo and M. Mohamed described a 34-year-old white man with a 4-day history of abrupt onset, negative paracentral scotoma in OD [10]. This occurred 16 days after he was diagnosed with COVID-19. Examination revealed normal fundoscopy, no uveitis, and normal VA. A rupture of the interdigitation zone and a focused area of faint OPL hyper-reflective alteration, indicative of acute macular neuroretinopathy, were detected. A link exists between D-dimers and ischaemia resulting from PAMM. The correlation between D-dimer readings and clinical ocular manifestations was documented by S.K. Padhy et al., who reported that the onset of PAMM in a 19-year-old female followed SARS-CoV-2, likely because of laboratory-confirmed increased D-dimer levels (post-COVID) for which she was medically administered corticosteroids [12]. D-dimer, a fibrin-degradation product, is frequently elevated in COVID-19 patients and is enhanced in thrombotic episodes, indicating fibrinolysis. Increased D-dimer readings correlate with disease severity and high death rates in these patients by activating the coagulation cascade because of the systemic inflammatory response syndrome. Before any relevant conclusions can be drawn, the association between D-dimer levels and PAMM in patients with COVID-19 must be scrutinised. Our patient developed an ischaemic stroke 1 year after PAMM.

Likewise, the exact cause of Krill’s disease is not fully understood. While some conditions, such as CMV retinitis, can cause inflammation and damage to the retina and the underlying tissue, there is no clear evidence that suggests a direct link between viral infections and Krill’s disease. Influenza-like symptoms occur before the onset of the disease, suggesting that viral infection may play a role in the pathogenesis. However, endothelial dysfunction in patients with COVID-19 resulting from increased expression of ACE-2 receptors could play a role in Krill’s disease. Thrombogenic events are rather common in COVID-19 patients [5]. In a 17-year-old woman with COVID-19, Walinjkar et al. described a dramatic case of CRVO [22, 24]. A 33-year-old woman who was previously healthy described a case identical to that described by Yahalomi et al. [24]. There have been several reports of CRAOs, which may be associated with viral-induced vasculitis and endothelial damage. Generally, thrombosis due to COVID-19 infection tends to occur in more severe cases and is often associated with other symptoms of the disease, such as respiratory distress or fever.

All patients were not vaccinated at the time of their clinical presentation, had relatively mild COVID-19 clinical features, and have not been taking corticosteroid therapy for COVID-19. They developed some complications of the posterior segment during the disease or immediately after (< 2 weeks maximum), which led us to believe that these could be possible complications of the disease. There is convincing evidence suggesting that the prothrombotic factors of COVID-19 and activation of the inflammatory cascade contribute to retinal alterations [5, 23]. Increased D-dimers, ACE-2 receptor expression, and tissue tropism of SARS-CoV-2 are known mechanisms. Patients should be monitored and asked for their visual
disturbances and assessed in the shortest possible time if they have symptoms because ocular symptoms may precede systemic manifestations of COVID-19. Additionally, they may serve as viable indicators preceding ischaemic or thrombotic retinal manifestations, allowing physicians to treat their patients before onerous symptoms arise. Vaccination lowers morbidity and mortality rates [2]. However, the COVID virus, in its various forms, is still ever-present, and at-risk patients should be carefully monitored for COVID-related pathologies, especially at-risk populations including hypertensive, diabetic, obese, and elderly patients.

Conclusion

The impact of COVID-19 on the manifestation of ocular pathologies has been a subject of growing concern in the ophthalmological community. This case series has shed light on various retinal pathologies, including CSCR, PAMM, bilateral Krill’s disease, and central retinal artery occlusion, which have been associated with the inflammatory and thrombotic effects of the SARS-CoV-2 virus on the retina.

These cases highlight the importance of early diagnosis and appropriate management to prevent vision loss in patients with ophthalmic manifestations. It is noteworthy that these pathologies are relatively rare complications of COVID-19, and not all individuals infected with the virus will experience such issues. However, the cases presented here provide insights into the potential mechanisms underlying these complications, including the role of immune response, stress hormones, ACE-2 receptors, and prothrombotic factors in the development of retinal abnormalities.

While further research is needed to establish a definitive correlation between these ophthalmic manifestations and COVID-19 infection, this case series underscores the importance of vigilance and timely clinical assessment in patients with COVID-19 infection, particularly those in at-risk populations. With the ongoing presence of COVID-19 and the emergence of new variants, continued monitoring and research are essential to better understand and address the ocular consequences of this pandemic.

Abbreviations

1. ACE-2: Angiotensin-converting enzyme 2
2. BCVA; VA: Best-Corrected Visual Acuity; Visual Acuity
3. CSCR: Central Serous Chorioretinopathy
4. CRAO: Central Retinal Artery Occlusion
5. DFE: Dilated Fundus Examination
6. EOG: Electrooculography
7. FAF: Fundus autofluorescence
8. FFA: Fundus Fluorescein Angiography
9. INL: Inner Nuclear Layer
10. IOP: Intraocular Pressure
11. IPL: Inner Plexiform Layer
12. mERG: Multifocal electroretinography
13. NSAID: Nonsteroidal anti-inflammatory drug
14. OD: Oculus Dexter (right eye)
15. OS: Oculus sinister (left eye)
16. OPL: Outer Plexiform Layer
17. PAMM: Paracentral Acute Middle Maculopathy
18. PCV: Polypoidal Choroidal Vasculopathy
19. RPE: Retinal Pigment Epithelium
20. SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
21. SD-OCT: Spectral Domain Optical Coherence Tomography
22. TMPRSS2: Transmembrane Protein Serine Protease 2

Declarations

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Contributions

E.G.O wrote the body of the manuscript. N.B.I. ensured appropriate figures were collected. I.J. refined and added to the introduction and discussion. N.D. and R.L. made the final edits and text insertions/deletions.
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Ethics declarations

Ethics approval and consent to participate

The procedures were performed according to the Declaration of Helsinki and were approved by the Ethics Committee of Svjetlost Eye Clinic. Written informed consent was obtained from all the participants and/or their legal guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

References


Figures
Figure 1
Parafoveal subretinal fluid in a patient with CSCR after COVID-19 infection.

Figure 2
Clarus imaging (A, B) demonstrates white lesions parafoveally and along the inferior arcade. Peripapillary and dot-blot haemorrhages were bilaterally observed in all 4 quadrants, along with ischaemic zones. SD-OCT shows bilateral placoid lesions in the inner retinal layers of the right eye.
Figure 3

A: Bilateral FAF imaging demonstrating hyperfluorescent and hypofluorescent lesions in the macular area and adjacent to the arcades.

B: Bilateral SD-OCT imaging demonstrating subfoveal RPE attenuation and associated retinal thickening.
Figure 4

SD-OCT imaging revealing ischaemic paramacular zones.