Posterior segment manifestations and imaging features of COVID-19

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ABSTRACT

Background: To report the posterior segment (uvea and retinal) manifestations and imaging characteristics of eyes of patients with and after coronavirus disease 2019 (COVID-19).

Methods: We searched the PubMed/MEDLINE database to identify relevant articles using the following search terms: COVID-19, SARS-CoV-2, retina, uvea, optic nerve, retinal findings, posterior segment manifestations, and endophthalmitis. Articles published from December 1, 2019, to May 30, 2021, and indexed in PubMed/MEDLINE were screened.

Results: For the purpose of this review, we included clinical features of 26 case reports and 8 case series. The posterior segment manifestations reported included cotton wool spots, retinal hemorrhages, central serous retinopathy, papillophlebitis, optic neuritis, panuveitis, multifocal retinitis, necrotizing retinitis, central retinal artery/vein occlusion, and Purtschner like retinopathy. In this review, we have also included optical coherence tomography angiography (OCTA) features that have been described in COVID-19 patients with pneumonia.

Conclusions: COVID-19 patients can experience uveo-retinal manifestations even after recovery. These patients, even if asymptomatic for eye symptoms, should undergo an eye evaluation to rule out posterior segment involvement. OCTA performed in these patients revealed microvascular changes in the superficial and deep retinal plexuses. Some of these patients may require anticoagulant or antiplatelet therapy.

KEYWORDS

SARS-CoV-2, COVID-19, ocular manifestations, posterior segment, uvea, retina, optical coherence tomography angiography

INTRODUCTION

Corona virus disease-19 (COVID-19) is caused by the highly contagious novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Early in the COVID-19 pandemic, most of the ocular manifestations reported were restricted to the anterior segment. Conjunctivitis and conjunctival congestion were the earliest reported features [2-5]. Systemically, COVID-19 may affect multiple organs, such as the lungs, heart, and kidneys, due to direct viral invasion as well as immune-mediated inflammation, which induces widespread
endotheliitis that may cause microvascular dysfunction and tissue ischemia [6].

In a study of hospitalized patients, only 31.6% reported ocular symptoms [3]. The clinical features included conjunctival hyperemia, chemosis, epiphora, or increased secretion. Patients with ocular manifestations of COVID-19 had higher white blood cell and neutrophil counts, and higher C-reactive protein (CRP), procalcitonin, and lactate dehydrogenase levels than COVID-19 patients without ocular abnormalities [3]. The presence of viral ribonucleic acid (RNA) in the retinas of patients who died of COVID-19 may support the hypothesis of possible virus-induced retinal vasculitis and ischemia [6].

This review aimed to collate data on posterior segment manifestations reported in patients who had contracted COVID-19 infection.

METHODS

We searched the PubMed/MEDLINE database from December 1, 2019, to May 30, 2021, to identify relevant articles using the following search terms: (“COVID-19” OR “SARS-CoV-2”) AND (“retina” OR “uvea” OR “optic nerve” OR “retinal findings” OR “posterior segment manifestations” OR “endophthalmitis”). The search yielded 53 articles. We screened articles based on titles and abstracts, and those more appropriate selected for inclusion in this review.

Furthermore, we have included figures from our patients with COVID-19 to illustrate the posterior segment manifestations of COVID-19 better. This study was approved by our hospital’s ethics committee. The study was approved by the Narayana Nethralaya Ethics Committee, with approval number EC reference NO C/2020/09/09 (virtual). The study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all our patients for inclusion of their data in the study.

RESULTS

We identified 34 records, comprising 26 individual case reports [9, 11, 13, 17-24, 26-37, 40-42] and 8 case series [7, 8, 10, 12, 14, 15, 38, 39] in this review, the main concepts of which are summarized in Table 1. Furthermore, we described optical coherence tomography angiography (OCTA) features seen in patients with COVID-19 pneumonia in the discussion wherever relevant.

DISCUSSION

Cotton wool spots (CWSs) (Figure 1) are the most common fundus findings reported in COVID-19 patients and may serve as an in vivo marker for imminent vascular events [7-15]. Retinal assessment may help in recognizing patients with possible arterial microangiopathy, in whom anticoagulants can play a therapeutic role. Vascular damage could be due to a hypercoagulable state and a vasculitis-like process secondary to direct viral infection of the endothelial cells and diffuse endothelial inflammation [7]. CWSs can occur in a broad spectrum of diseases, such as hypertension and other diseases; thus, baseline and serial monitoring is important for clinical interpretation and management [16].
## Table 1. Summary of the posterior segment manifestations and ocular imaging features of COVID-19, in published case reports or case series, from the start of the COVID-19 pandemic up to May 2021

<table>
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<tr>
<th>Authors/Year</th>
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<tbody>
<tr>
<td>Landecho et al. (2020) [7]</td>
<td>27</td>
<td>Median age: 56 y; M/F: 18:9</td>
<td>43 d</td>
<td>None</td>
<td>CWS, swelling of the RNFL</td>
<td>OCT: swelling of the RNFL</td>
<td>N/A</td>
</tr>
<tr>
<td>Marinho et al. (2020) [8]</td>
<td>12</td>
<td>Range: 25-69 y; M/F: 6:6</td>
<td>None</td>
<td>CWS and micro-retinal hemorrhages</td>
<td>OCT: hyperreflective lesions at the level of the GCL and IPL, more prominently at the PME in BE</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Insausti-García et al. (2020) [9]</td>
<td>1</td>
<td>30 y; M</td>
<td>6 weeks</td>
<td>Persistent and variable ROPV in LE</td>
<td>Inflammation of the ONH, Retinal venous vasodilatation and tortuosity, CWS, superficial hemorrhages</td>
<td>FA: discrete venous staining and leakage from the optic disc, OCT: hyperreflective lesions at the level of the GCL and IPL, more prominently at the PME in BE, HFA: diffuse sensitivity decrease, associated with a slight central scotoma, OCT: papillary edema without evidence of involvement of the macular area</td>
<td>N/A</td>
</tr>
<tr>
<td>Invernizzi et al. (2020) [10]</td>
<td>54</td>
<td>Mean: 49.9 y; M/F: 38:16</td>
<td>None</td>
<td>BOV, redness, photophobia, burning sensation</td>
<td>Hemorrhages, CWS, dilated veins, tortuous vessels, and drusen</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Lopez et al. (2020) [11]</td>
<td>1</td>
<td>50 y; M</td>
<td>17 d</td>
<td>Inferior, crescent-shaped scotoma</td>
<td>CWS, subtle white lesions at macula, bilaterally</td>
<td>OCT: presence of focal hyperreflective changes in IPL, OPL, with significant hyperreflective plaques in the macula, OCTA: decreased capillary flow in the superficial retinal plexus</td>
<td>N/A</td>
</tr>
<tr>
<td>Invernizzi et al. (2020) [12]</td>
<td>25</td>
<td>Mean: 51.2 y; M/F: 16:9</td>
<td>None</td>
<td>Hemorrhages</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pereira et al. (2020) [14]</td>
<td>18</td>
<td>Median: 62.5 y; M/F: 10:8</td>
<td>11 d</td>
<td>None</td>
<td>Hemorrhages and CWS, RPE hyperplasia, and hard exudates</td>
<td>OCT: thickening and hyperreflectivity of the RNFL</td>
<td>N/A</td>
</tr>
<tr>
<td>Sim et al. (2020) [15]</td>
<td>108</td>
<td>Mean: 36 y</td>
<td>None</td>
<td>Micro-hemorrhages, retinal vascular tortuosity, CWS</td>
<td>Hyper-reflective plaques in the GCL-IPL on OCT</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Bottini et al. (2021) [17]</td>
<td>1</td>
<td>59 y; M</td>
<td>42 d</td>
<td>BOV, BE</td>
<td>Multiple foci of inner retinal opacification, CWS</td>
<td>OCTA at SCP demonstrated flow voids corresponding to the location of the OCTA, OCT: irregularity of the RPE and OPL, OCT: irregularity of the RPE and OPL</td>
<td>N/A</td>
</tr>
<tr>
<td>Benito-Pascual et al. (2020) [18]</td>
<td>1</td>
<td>60 y; F</td>
<td>Two weeks</td>
<td>Ocular pain</td>
<td>OCTA: prominent optic nerve head edema, peripapillary choroidal folds</td>
<td>OCTA: prominent optic nerve head edema, peripapillary choroidal folds</td>
<td>N/A</td>
</tr>
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</table>
Continued Table 1. Summary of the posterior segment manifestations and ocular imaging features of COVID-19, in published case reports or case series, from the start of the COVID-19 pandemic up to May 2021

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<tr>
<td>Acharya et al. (2020) [19]</td>
<td>1</td>
<td>60 y; M</td>
<td>12 d</td>
<td>Painless sudden VL in RE</td>
<td>RAPD; CRAO</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Sanjay et al. (2021) [20]</td>
<td>1</td>
<td>66 y; M</td>
<td>3 d</td>
<td>BE BOV (RE &gt; LE)</td>
<td>CRAO with CWS, hemorrhages, disc edema and -2 hyperemia, and cystoid changes</td>
<td>OCT: increased reflectivity and thickness of the inner retinal layers, shadowing of the outer retinal layers, and a normal foveal contour FFA: early hypofluorescence with late hyperfluorescent rim and perivascular leak, and disc staining and leakage</td>
<td>N/A</td>
</tr>
<tr>
<td>Sawalha et al. (2020) [21]</td>
<td>1</td>
<td>44 y; M</td>
<td>14 d</td>
<td>Bilateral eye pain and VL</td>
<td>RAPD, superior arcuate visual field defect</td>
<td>N/A</td>
<td>Complete restoration of LE vision with remarkable vision recovery in the RE</td>
</tr>
<tr>
<td>Rho J et al (2020) [22]</td>
<td>1</td>
<td>43 y; M</td>
<td>14 d</td>
<td>Inferior painless VL</td>
<td>RAPD, microaneurysms, temporal pallor</td>
<td>HFA: dense inferior altitudinal defect that respects the horizontal meridian</td>
<td>N/A</td>
</tr>
<tr>
<td>Montesel (2020) [23]</td>
<td>1</td>
<td>59 y; M</td>
<td>22 d</td>
<td>VL in LE</td>
<td>CRAO, peripheral areas of RPE hyperpigmentation</td>
<td>FFA: severe delay in the filling of the retinal arteries and a delayed AV transit time, areas of peripheral capillary nonperfusion, AV anastomoses, and neovascular sea-fans</td>
<td>After 1 month, vision improved to counting fingers</td>
</tr>
<tr>
<td>Larochelle et al. (2021) [24]</td>
<td>1</td>
<td>58 y; M</td>
<td>16 hours earlier</td>
<td>VL in RE</td>
<td>RAPD, complete right abduction defect, and a -2 deficit of right supraduction, CRAO</td>
<td>N/A</td>
<td>Patient succumbed to his illness</td>
</tr>
<tr>
<td>Bapaye et al. (2021) [26]</td>
<td>1</td>
<td>42 y; M</td>
<td>14 d</td>
<td>Sudden VL in BE</td>
<td>CRAO</td>
<td>FFA: at presentation, normal reperfusion in the early phase, with disc staining with focal areas of choroidal hyperfluorescence temporally in the late phase OCT: thickened inner retinal layers suggestive of retinal edema, while the outer retinal layers appeared intact</td>
<td>N/A</td>
</tr>
<tr>
<td>Virgo and Mohamed (2020) [27]</td>
<td>2</td>
<td>37 y; F</td>
<td>35 d</td>
<td>Para-central scotoma</td>
<td>Normal fundoscopy</td>
<td>OCT: Focal area of hyper-reflective change in IPL and OPL, with INL volume-loss consistent with PAMM</td>
<td>N/A</td>
</tr>
<tr>
<td>Gascon et al. (2020) [28]</td>
<td>1</td>
<td>53 y; M</td>
<td>8 d</td>
<td>Negative scotoma and dyschromatopsia</td>
<td>Hemorrhages and Roth spots, and subtle whitish parafoveal lesions</td>
<td>HFA 10–2 test: paracentral scotoma SD-OCT through the foveal lesion revealed multiple hyperreflective bands at the boundary of the OPL and INL that extended into the INL, which were consistent with PAMM, OPL, HFL, ONL, EZ/IZ attenuated. Associated with SRF consistent with AMN. OCT, areas of decreased flow signal that were more prominent in the DCP than SCP FFA: masking of retinal hemorrhages with out vasculitis associated with discrete ONH staining in the late phase.</td>
<td>After 4-d: SD-OCT showed decrease of the SRF, worsening of EZ/IZ disruption and persistence of PAMM lesions</td>
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<tr>
<td>Zamani et al. (2021) [29]</td>
<td>1</td>
<td>35 y; F</td>
<td>N/A</td>
<td>Sudden painless paracentral visual field defect and photopsia</td>
<td>Hemorrhages and Roth spots around the optic disk and vascular arcades in BE</td>
<td>OCT: hyper-reflectivity of the ONL and OPL associated with attenuation of the EZ nasal to the fovea of the RE. Outer retina segmentation en-face OCT revealed hyper-reflective patch</td>
<td>Patient died after 6 days because of severe pneumonia</td>
</tr>
<tr>
<td>Invernizzi et al. (2020) [30]</td>
<td>1</td>
<td>54 y; F</td>
<td>10 d</td>
<td>Scotomas and BOV</td>
<td>CRVO</td>
<td>OCT: hyperreflectivity of the inner retinal layers FA: typical distribution of the retinal alteration showing perivenular hypo-autofluorescence FFA: delayed AV transit time</td>
<td>After 1 week: multimodal imaging revealed an almost complete regression of the retinal alterations</td>
</tr>
<tr>
<td>Waljinkar et al. (2020) [31]</td>
<td>1</td>
<td>17 y; F</td>
<td>21 d</td>
<td>BOV and flashes of light</td>
<td>Optic disc swelling with hemorrhages</td>
<td>OCT: neurosensory detachment and CME</td>
<td>After 1 month, significant resolution of signs of CRVO</td>
</tr>
<tr>
<td>Yahalomi et al. (2020) [32]</td>
<td>1</td>
<td>33 y; M</td>
<td>14 d</td>
<td>BOV and flashes of light</td>
<td>CRVO with optic disc edema</td>
<td>FFA: marked delay in AV transit time, staining of dilated tortuous veins, and masking by retinal hemorrhages.</td>
<td>Frequent follow up</td>
</tr>
<tr>
<td>Venkatesh et al. [33]</td>
<td>1</td>
<td>56 y; F</td>
<td>N/A</td>
<td>BOV</td>
<td>Non-ischemic CRVO and macular edema</td>
<td>OCT LE, CME, NSD</td>
<td>After 1 month: complete resolution of CME on OCT</td>
</tr>
<tr>
<td>Sheth et al. [34]</td>
<td>1</td>
<td>52 y; M</td>
<td>10 d</td>
<td>BOV</td>
<td>Retinal vein occlusion with macular edema</td>
<td>FFA: 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 SD-OCT: presence of SMD in the LE</td>
<td>After 1 month: complete resolution of SMD and CME on SD-OCT</td>
</tr>
<tr>
<td>Finn et al. (2020) [35]</td>
<td>1</td>
<td>32 y; M</td>
<td>30 d</td>
<td>Para central scotoma,</td>
<td>Retinal hemorrhages, and dilated and tortuous retinal vessels inferiorly</td>
<td>FFA: RE shows marked delay in filling of the inferior venous circulation with late staining of vessels OCT: RE shows no evidence of central macular edema, mild thickening and increased hyperreflectivity of the OPL nasally</td>
<td>N/A</td>
</tr>
<tr>
<td>Filho et al. (2020) [36]</td>
<td>1</td>
<td>57 y; F</td>
<td>12 d</td>
<td>Eye redness</td>
<td>Conjunctival hyperemia, vitritis, yellowish lesion within the macular area</td>
<td>FFA: revealed hyperfluorescence SD-OCT: hyperreflective pinpoints at the level of the posterior vitreous hyaloid corresponding to vitritis, hyperreflective lesions at the level of the IPL and GCL, and disruption of the EZ</td>
<td>After 2 months: a decrease in the retinal lesions’ reflectivity and size</td>
</tr>
<tr>
<td>Gupta et al. (2020) [37]</td>
<td>1</td>
<td>75 y; F</td>
<td>21 d</td>
<td>Floaters, BOV</td>
<td>RE: superior peripheral retinitis with minimal anterior or vitreous inflammation LE: panuveitis, vitritis, and extensive peripheral and mid-peripheral necrotizing retinitis</td>
<td>N/A</td>
<td>After 2 months: viral retinitis significantly improved. LE continued to have poor vision due to retinal thinning and the development of a cataract</td>
</tr>
<tr>
<td>Shah et al. (2021) [38]</td>
<td>4</td>
<td>Range: 54 to 64 y; M/F: 4:0</td>
<td>14-45 d</td>
<td>BOV, ocular pain, central scotoma, and black dots</td>
<td>Subretinal exudate, and abscess, vitreous exudates</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Goyal M et al (2021)</td>
<td>7</td>
<td>Range: 23 to 75 y; M/F: 4:3</td>
<td>Four patients: onset of symptoms during the active phase. Four bilateral and three had unilateral involvement.</td>
<td>N/A</td>
<td>Endogenous endophthalmitis, candida retinitis, and tubular choroidal abscess, bilateral pre-foveal hemorrhages, paracentral acute middle maculopathy, central serous chorioretinopathy, and voriconazole induced visual symptoms</td>
<td>OCT findings in different cases revealed vitreous traction over the lesion, showed disruption in the outer retinal layers, hyperreflective lesions in superficial retinal layers with shadowing of deeper retina, serous detachment of macula HVP: normal in one patient</td>
<td>Final VA: 20/120 or better in four severe cases and 20/320 or better in mild cases.</td>
</tr>
<tr>
<td>Providencia et al. (2020)</td>
<td>1</td>
<td>41 y; F</td>
<td>30 d</td>
<td>BOV, metamorphopsia</td>
<td>Multiple peripapillary atrophic lesions and a larger diffuse, yellowish-white deep amoeboid-like patch, with indistinct margins, extending temporally to the fovea</td>
<td>ICG: peripapillary lesions appeared hypoautofluorescent in early and late phases FFA: early hypofluorescence of lesions, with late staining of atrophic lesions and leakage of the border approaching the fovea, nasal and inferiorly FA: multiple hypoautofluorescent peripapillary lesions, corresponding to the older atrophic lesions, and a serpiginous-like patch of hyper-autofluorescence approaching the foveal region</td>
<td>Early follow-up period: the described active lesion LE started to fade, and VA LE improved to 20/100</td>
</tr>
<tr>
<td>Sanjay et al. (2021)</td>
<td>1</td>
<td>42 y; F</td>
<td>12 d</td>
<td>BOV</td>
<td>Central serous retinopathy</td>
<td>OCT: hyperreflective dots in the posterior vitreous, altered foveal contour with SMD and PED RE FFA: multiple hyperfluorescent spots seen in the macula which increased in size and intensity in later films in an inkblot pattern</td>
<td>OCT: reduction of the subretinal fluid and the hyperreflective material and resolution of the PED</td>
</tr>
<tr>
<td>Sharma et al. (2021)</td>
<td>1</td>
<td>22 y; F</td>
<td>14 d</td>
<td>BOV in the inferior field</td>
<td>Optic disc edema (parainfectious optic neuritis) and retinal vessel tortuosity</td>
<td>HFA: inferior feld defect OCT: on ONH OCT, RNFL was thicker than the mean superior, nasal, and inferior quadrants. However, brain/orbit/spine imaging were within normal limits</td>
<td>Subjective resolution of scotoma following treatment</td>
</tr>
</tbody>
</table>

: n, number; Onset, onset of symptoms; y, years; M, male; F, female; d, days; CWS, Cotton wool spots; OCT, Optical coherence tomography; RNFL, Retinal nerve fibre layer; N/A, not available; GCL, ganglion cell layer; IPL, inner plexiform layer; PMB, papillomacular bundle; BE, both eyes; ONH, optic nerve head; BOV, blurring of vision; LE, left eye; FFA, fundus fluorescein angiography; HFA, humphrey field analyzer; SS-OCT, swept source optical coherence tomography; OCTA, optical coherence tomography angiography; OPL, outer plexiform layer; INL, inner nuclear layer; PAMM, paracentral acute middle maculopathy; RPE, retinal pigment epithelium; SCP, superficial capillary plexus; RAPD, afferent papillary defect; VL, vision loss; CRAO, central retinal artery occlusion; AMN, acute macular neuroretinopathy; HFL, helix fiber layer; ONL, outer nuclear layer; EZ, ellipsoid; IZ, interdigitation zones; DCF, deep capillary plexus; SRF, Subretinal fluid; CRVO, central retinal vein occlusion; AV, arteriovenous; FAF, fundus autoflorescence; CME, cystoid macular edema; NSD, neurosensory detachment; SMD, serous macular detachment; VA, visual acuity; ICG, indocyanine green angiography; PED, pigment epithelial detachment.
The posterior segment manifestations reported in COVID-19 patients include CWSs (Figure 1 and 2), retinal hemorrhages, central serous retinopathy, papillophlebitis, optic neuritis, optic atrophy, panuveitis, multi-focal retinitis, necrotizing retinitis, central retinal artery/vein occlusion, and Purtscher-like retinopathy [17-21, 42]. Bilateral CWSs localized to the posterior pole revealed retinal nerve fiber layer (RNFL) infarcts on multimodal imaging, which was consistent with a Purtscher-like retinopathy, in a 59-year male with COVID-19 [17].

Optic nerve inflammation associated with COVID-19 has been reported and is presumed to be due to an immune-mediated response and deranged coagulation mechanisms [9, 18-21]. A 43-year-old Hispanic male with diabetes and borderline hyperlipidemia developed non-arteritic anterior ischemic optic neuropathy (NAION) after COVID-19. It was postulated that patients with COVID-19 infection can manifest with hypercoagulability and hypoxemia, both of which may contribute to the development of NAION. Diabetic patients had a risk of developing NAION, and COVID-19 altered the auto-regulatory mechanisms of optic nerve perfusion, resulting in NAION. However, this relationship may be incidental, and it is difficult to establish a causal role [22].

Bikdeli et al. [25] suggested that COVID-19 may predispose patients to arterial and venous thrombosis. Multiple case reports of retinal vascular occlusion have been reported [19-31]. Acharya et al. [19] reported the first case of isolated central retinal artery occlusion (CRAO) secondary to COVID-19. We reported on a patient who had unilateral CRAO associated with bilateral panuveitis and papillitis after COVID-19 [20]. Bilateral CRAO after COVID-19 was reported in a patient who had been investigated for vasculitis, coagulation profile, lipids, and homocysteine levels [26]. In some patients with retinal vascular occlusions, markers such as interleukin-6, CRP, ferritin, fibrinogen, and D-dimer, imply a prothrombotic and hypercoagulable state [19, 20, 25, 26].

Recent-onset paracentral scotoma has been found after COVID-19 in patients who were diagnosed with paracentral acute middle maculopathy and acute macular neuroretinopathy based on imaging findings [13, 27-29]. Postulated mechanisms include ischemia of the deep capillary plexus (DCP), and may theoretically be seen in any patient with retinal vascular disease or systemic vascular risk factors. Central retinal vein occlusion
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CRVO has been reported in four cases [30-33] (Figure 3) and hemi-retinal vein occlusion in two cases [34].

Vitreous inflammation and panuveitis have also been reported in COVID-19 cases [18, 20, 36, 37]. Figure 3 shows a patient with a left CRVO. In a 57-year-old woman from Brazil who had no anterior chamber inflammation, optical coherence tomography (OCT) revealed posterior vitreous cells and inner and outer retinal involvement [36]. A 75-year-old woman with COVID-19 who had recently completed chemotherapy for diffuse large B-cell lymphoma developed vitritis and panuveitis with necrotizing retinitis (Table 1). Her vitreous sample was subjected to polymerase chain reaction (PCR), which tested positive for varicella zoster virus but negative for SARS-CoV-2 [37].

Presumed fungal endophthalmitis has been reported in COVID-19 cases. Four male patients, two of whom suffered from diabetes mellitus, had vitritis and subretinal exudates, with no identifiable organism found either in the eye or systemically [38]. Another series of seven COVID-19 patients had uveo-retinal manifestations with good visual prognosis (Table 1) [39]. COVID-19 infection may play a role as a possible trigger of intraocular inflammation in patients with serpiginous choroiditis [40].

We have reported that long-term use of oral and inhalational steroids following COVID-19 infection can predispose patients to central serous retinopathy (CSR) (Figure 4) [41].

Optical coherence tomography angiography (OCTA) may offer clues to retinal vascular circulation. In a study on retinal microvascular impairment using OCTA in patients with COVID-19 bilateral pneumonia, González-Zamora et al. [43] showed that the superficial and deep choroid plexuses (SCP and DCP, respectively) had decreased vascular density and the foveal avascular zone (FAZ) was enlarged in the perifoveal capillary network. However, the choriocapillaris was spared. In their optic nerve head analysis, a significantly thicker RNFL was found in COVID-19 patients with CWS than in those without CWS. Cennamo et al. [44] in their case-control study had similar findings in the SCP and DCP. However, the ganglion cell complex showed no difference between the groups. Nevertheless, there was a significant difference in RNFL and radial peripapillary capillaries between COVID-19 patients and healthy controls. They suggested the possibility of using OCTA as a biomarker of early vascular dysfunction after COVID-19 infection [44]. Abrishami et al. [45] found that vessel densities in the foveal and parafoveal regions in both the SCP and DCP were lower than in the healthy controls. Similar to the study by González-Zamora et al. [43], they found a greater FAZ area in the COVID-19 cohort, but this difference was not statistically significant. The vessel density of the SCP in their series was lower in patients who had been hospitalized for COVID-19 than in those who were not [43]. Turkay et al. [46] reported similar findings in a 6-month follow-up OCTA study of 50 eyes of 25 COVID-19 patients. One significant finding was that the choriocapillaris flow area values were significantly lower at the 6-month follow-up than at the initial examination.

SARS-CoV-2 is reported to have neuroendothelial tropism [47, 48]. When SARS-CoV2 infection occurs, it may lead to the downregulation of angiotensin-converting enzyme-related carboxypeptidase (ACE2) receptor, which is expressed in multiple organs, including the lungs, heart, kidneys, arteries, and veins [49, 50, 51]. This receptor is also present in ocular structures, such as the conjunctiva, retinal pigment epithelium, retina, and choroid [52]. Endothelial cells express high levels of ACE2 receptors, which make them vulnerable...
to SARS-CoV2 infection [53]. Endothelial dysfunction can lead to microvascular disturbances.

Whether the coagulation cascade dysfunction is caused by the virus itself or is the result of local or systemic inflammation secondary to the infection is not yet understood [54]. Hypercoagulability is a major cause of morbidity and mortality in patients with COVID-19, with reports of deep venous thrombosis, pulmonary emboli, and large-vessel ischemic strokes [55, 56]. A similar mechanism of immune-mediated inflammation of the endothelium of the retinal vasculature may lead to edema and thrombosis of smaller vessels, with subsequent ischemia leading to retinal damage [6].

There is no universal consensus on the optimal management of posterior segment manifestations of COVID-19. Treatment options include use of ocular or systemic medications. Oral acetyl salicylic acid can be considered for retinal vascular occlusions. Intravitreal steroid/steroid implants may play a therapeutic role in retinal vein occlusion [18]. Oral or inhalational steroids may need to be discontinued in patients with CSR [40].

In cases of inflammatory conditions, such as panuveitis, serpiginous choroiditis, and optic neuritis, oral/intravenous or topical steroids with immunosuppression are treatment options [19, 39]. However, caution is needed, as infections must be ruled out before considering steroid use or immunosuppression [38]. Oral/topical/intravitreal antifungals have been used for presumed endogenous endophthalmitis [39]. We also encountered a case of endogenous endophthalmitis in whom anterior chamber tap PCR was positive for Eubacteria (Figure 5). Systemic/intravitreal antivirals may play a therapeutic role in necrotizing retinitis [37]. Pars plana vitrectomy may be required for sight-threatening infections [38].

In this review, we have included most of the commonly reported posterior segment manifestations following COVID-19 reported up to May 30, 2021, as summarized as a reference source in Table 1. We have also included a description of our representative cases. However, a systematic search using all MeSH and Emtree terms was not performed. We have highlighted only the manifestations that we found were relevant to clinical practice. We aimed to include more molecular diagnostics along with clinical features to explain them.
Figure 5. A 47-year-old Indian male, who was COVID-19-positive with no other systemic illness, developed right eye visual blurring 3 weeks after COVID-19 diagnosis and was diagnosed as having endogenous endophthalmitis. The diffuse slit lamp image of the right eye (figure on the left) shows ciliary congestion, hazy cornea, anterior chamber exudates, and fibrinous reaction, and posterior synechiae of the iris with a pupillary membrane. The ultrasound B scan image of his right eye (top, right) shows hyperreflective membranes in the entire vitreous cavity. The right, bottom image shows pre- and subretinal exudates. He underwent anterior chamber tap polymerase chain reaction, which was positive for Eubacteria, and he had a raised SARS-CoV-2 IgM/IgG total antibody titer.

Future systematic reviews focusing on the rate of posterior segment manifestations with a comprehensive search of more databases could provide more conclusive outcomes.

CONCLUSIONS

COVID-19 patients can experience uveo-retinal manifestations even after recovery and should undergo long-term follow-up to monitor for signs of retinal vascular manifestations and sequelae. These patients, even if asymptomatic for eye symptoms, should undergo a detailed eye evaluation to rule out retinal involvement. A fundus evaluation may help to detect those patients with signs of arterial microangiopathy in whom antiplatelet aggregation therapy or anticoagulants may be indicated. OCTA is a non-invasive and useful modality that may offer clues to the state of retinal circulation, even in asymptomatic COVID-19 patients.

ETHICAL DECLARATIONS

Ethical approval: The study was approved by the hospital ethics committee. The study was approved by the Narayana Nethralaya Ethics committee, with approval number EC reference NO C/2020/09/09 (virtual). All tenets of the Helsinki declaration were adhered to. Patient’s written and informed consent was obtained for inclusion in the study.

Conflict of Interests: None

FUNDING

None.

ACKNOWLEDGEMENTS

Dr. Srinivasan Sanjay, Dr. Poornachandra B. Gowda, Dr. Vishma Prabhu, and Dr. Ramesh Venkatesh provided clinical photographs. Figure 4 has been reused from J Ophthal Inflamm Infect, a journal from Springer Nature, with permission under the Creative Commons Attribution v4.0 International license (CC BY).[41]
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