Review Article

Posterior segment manifestations and imaging features post–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.

KEY WORDS

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

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

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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].

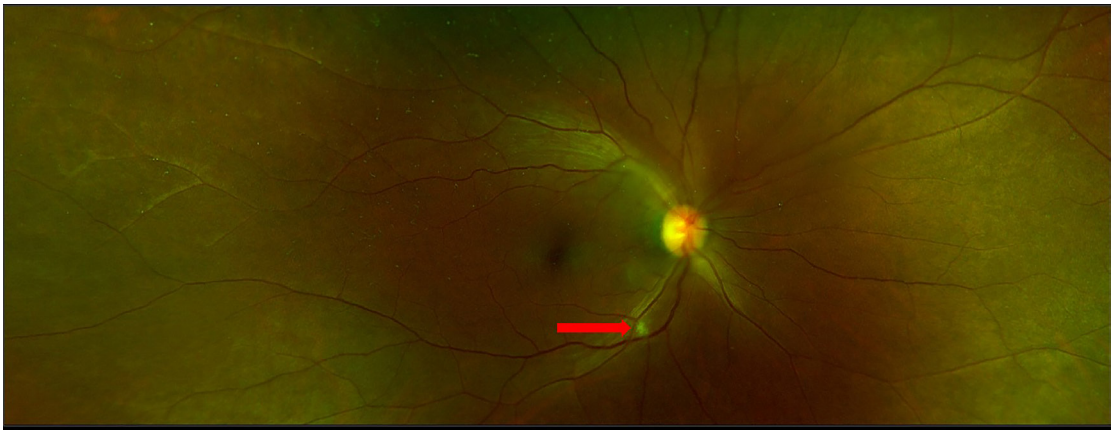

Figure 1. A 48-year-old Asian Indian female presented with right upper lid ptosis. Her best corrected visual acuity in both eyes were 20/20. Her diabetes was under control, and she had no previous diabetic retinopathy. She had been diagnosed with COVID-19 infection a month earlier and had received supportive treatment at the local hospital. Wide-field fundus imaging of the right eye with Optos™ (Optos P200DTx icg, Optos, Marlborough, MA, USA) showed an isolated cotton wool spot in the right eye (red arrow) with no other evidence of diabetic retinopathy in either eye.

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

Authors/Year	n	Age/Sex	Onset	Ocular Symptoms	Ocular Signs	Findings on Imaging	Follow up
Landecho et al. (2020) [7]	27	Median age: 56 y; M/F: 18:9	Mean: 43 d	None	CWS	OCT: swelling of the RNFL	N/A
Marinho et al. (2020) [8]	12	Range: 25-69 y; M/F: 6:6	11-33 d	None	CWS and micro retinal hemorrhages	OCT: hyperreflective lesions at the level of the GCL and IPL, more prominently at the PMB in BE	N/A
Insausti-García et al. (2020) [9]	1	40 y; M	6 weeks	Persistent and painless BOV in LE	Inflammation of the ONH. Retinal venous vasodilatation and tortuosity, CWS, and superficial hemorrhages	FA: discrete venous staining and leakage in the acute phase, leakage and late staining from the optic disc OCT: papillary edema without evidence of involvement of the macular area HFA: diffuse sensitivity decrease, associated with a slight central scotoma and moderate increase in the blind spot	After 2 weeks: a marked decrease in macular and disc edema, and VA: 20/40
Invernizzi et al. (2020) [10]	54	Mean: 49.9 y; M/F: 38:16	Mean: 13.6 d	BOV, redness, photophobia, burning sensation	Hemorrhages, CWS, dilated veins, tortuous vessels, and drusen	N/A	N/A
Lopez et al. (2020) [11]	1	50 y; M	17 d	Inferior, crescent-shaped scotoma	CWS	SS-OCT: over the lesions showing RNFL edema, there is disruption of the normal reflectivity of the nuclear and plexiform retinal layers in the largest lesion OCTA: decreased capillary flow in the superficial retinal plexus over the lesion areas HFA: inferior arcuate scotoma in LE, consistent with the most prominent retinal lesions	After 2 weeks: the LE scotoma had improved slightly in the HFA, although the CWS remained visible
Lani-Louzada et al. (2020) [12]	25	Mean: 51.2 y; M/F: 16:9	N/A	N/A	CWS, hemorrhages	N/A	N/A
Padhy et al. (2021) [13]	1	19 y; F	14 d	BE acute onset scotoma	CWS, subtle white lesions at macula, bilaterally	OCT: presence of focal hyper-reflective changes in IPL, OPL, with INL volume loss parafoveally; features consistent with PAMM	After 4 weeks: BE OCT; thinning of INL with irregularity of the IPL and OPL along with resolution of the CWS
Pereira et al. (2020) [14]	18	Median: 62.5 y; M/F: 9:9	11 d	None	Hemorrhages and CWS, RPE hyperplasia, and hard exudates	N/A	N/A
Sim et al. (2020) [15]	108	Mean: 36 y	N/A	N/A	Micro-hemorrhages, retinal vascular tortuosity, CWS	Hyper-reflective plaques in the GCL-IPL on OCT	N/A
Bottini et al (2021) [17]	1	59 y; M	42 d	BOV BE	Multiple foci of inner retinal opacification, CWS	OCT: thickening and hyper-reflectivity of the RNFL FFA: mild obscuration of the retinal vasculature OCTA at SCP demonstrated flow voids corresponding to the location of the lesions	After 2 months: Marked reduction in the size and number of CWS
Benito-Pascual et al. (2020) [18]	1	60 y; F	Two weeks	Ocular pain, BOV, and redness in the LE	RAPD, panuveitis, optic nerve swelling, peripapillary subretinal fluid, and peripapillary choroidal folds	OCT: edema of the RNFL	After 2 weeks: no signs of uveitis, vitritis or papillitis. Severe optic atrophy

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Authors/Year	n	Age/Sex	Onset	Ocular Symptoms	Ocular Signs	Findings on Imaging	Follow up
Acharya et al. (2020) [19]	1	60 y; M	12 d	Painless sudden VL in RE	RAPD; CRAO	N/A	N/A
Sanjay et al. (2021) [20]	1	66 y; M	3 d	BE BOV (RE > LE)	CRAO with CWS, hemorrhages, disc edema and hyperemia, and cystoid changes	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	N/A
Sawalha et al. (2020) [21]	1	44 y; M	14 d	Bilateral eye pain and VL	RAPD, superior arcuate visual field defect	N/A	Complete restoration of LE vision with remarkable vision recovery in the RE
Rho J et al (2020) [22]	1	43 y; M	14 d	Inferior painless VL	RAPD, microaneurysms, temporal pallor	HFA: dense inferior altitudinal defect that respects the horizontal meridian	N/A
Montesel (2020) [23]	1	59 y; M	22 d	VL in LE	CRAO, peripheral areas of RPE hyperpigmentation	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	After 1 month, vision improved to counting fingers
Larochelle et al. (2021) [24]	1	58 y; M	16 hours earlier	VL in RE	RAPD, complete right abduction deficit, and a -2 deficit of right supraduction, CRAO	N/A	Patient succumbed to his illness
Bapaye et al. (2021) [26]	1	42 y; M	14 d	Sudden VL in BE	CRAO	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	N/A
Virgo and Mohamed (2020) [27]	2	37 y; F	35 d	Para-central scotoma	Normal fundoscopy	OCT: Focal area of hyper-reflective change in IPL and OPL, with INL volume-loss consistent with PAMM	N/A
		32 y; M	16 d	Para-central scotoma	Normal fundoscopy	Changes on infrared reflectance OCT: A focal area of faint OPL, hyper-reflective change, and disruption of the interdigitation zone consistent with AMN	N/A
Gascon et al. (2020) [28]	1	53 y; M	8 d	Negative scotoma and dyschromatopsia	Hemorrhages and Roth spots, and subtle whitish parafoveal lesions	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 without vasculitis associated with discrete ONH staining in the late phase.	After 4-d: SD-OCT showed decrease of the SRF, worsening of EZ/IZ disruption and persistence of PAMM lesions

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

Authors/Year	n	Age/Sex	Onset	Ocular Symptoms	Ocular Signs	Findings on Imaging	Follow up
Zamani et al. (2021) [29]	1	35 y; F	N/A	Sudden painless paracentral visual field defect and photopsia	Hemorrhages and Roth spots around the optic disk and vascular arcades in BE	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	Patient died after 6 days because of severe pneumonia
Invernizzi et al. (2020) [30]	1	54 y; F	10 d	Scotomas and BOV	CRVO	OCT: hyperreflectivity of the inner retinal layers FAF: typical distribution of the retinal alteration showing perivenular hypo-autofluorescence FFA: delayed AV transit time	After 1 week: multimodal imaging revealed an almost complete regression of the retinal alterations
Waljinkar et al. (2020) [31]	1	17 y; F	21 d	BOV	Optic disc swelling with hemorrhages	OCT: neurosensory detachment and CME	After 1 month, significant resolution of signs of CRVO
Yahalomi et al. (2020) [32]	1	33 y; M	14 d	BOV and flashes of light	CRVO with optic disc edema	FFA: marked delay in AV transit time, staining of dilated tortuous veins, and masking by retinal hemorrhages.	Frequent follow up
Venkatesh et al. [33]	1	56 y; F	N/A	BOV	Non-ischemic CRVO and macular edema	OCT LE, CME, NSD	After 1 month: complete resolution of CME on OCT
Sheth et al. [34]	1	52 y; M	10 d	BOV	Retinal vein occlusion with macular edema	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	After 1 month: complete resolution of SMD and CME on SD-OCT
Finn et al. (2020) [35]	1	32 y; M	30 d	Paracentral scotoma,	Retinal hemorrhages, and dilated and tortuous retinal vessels inferiorly	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	N/A
Filho et al. (2020) [36]	1	57 y; F	12 d	Eye redness	Conjunctival hyperemia, vitritis, yellowish lesion within the macular area	FFA: revealed hyperfluorescence SD-OCT: hyperreflective pinpoints at the level of posterior vitreous hyaloid corresponding to vitritis, hyperreflective lesions at the level of the IPL and GCL, and disruption of the EZ	After 2 months: a decrease in the retinal lesions' reflectivity and size
Gupta et al. (2020) [37]	1	75 y; F	21 d	Floaters, BOV	RE: superior peripheral retinitis with minimal anterior or vitreous inflammation LE: panuveitis, vitritis, and extensive peripheral and mid-peripheral necrotizing retinitis	N/A	After 2 months: viral retinitis significantly improved. LE continued to have poor vision due to retinal thinning and the development of a cataract
Shah et al. (2021) [38]	4	Range: 54 to 64 y; M/F: 4:0	14-45 d	BOV, ocular pain, central scotoma, and black dots	Subretinal exudate, and abscess, vitreous exudates	N/A	N/A

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

Authors/ Year	n	Age/Sex	Onset	Ocular Symptoms	Ocular Signs	Findings on Imaging	Follow up
Goyal M et al (2021) [39]	7	Range: 23 to 75 y; M/F: 4:3	Four patients: onset of symptoms during the active phase. Four bilateral and three had unilateral involvement.	N/A	Endogenous endophthalmitis, candida retinitis, and tubercular choroidal abscess, bilateral pre-foveal hemorrhages, paracentral acute middle maculopathy, central serous chorioretinopathy, and voriconazole induced visual symptoms	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 HVF: normal in one patient	Final VA: 20/120 or better in four severe cases and 20/32 or better in mild cases.
Providencia et al. (2020) [40]	1	41y; F	30 d	BOV, metamorphopsia	Multiple peripapillary atrophic lesions and a larger diffuse, yellowish-white deep amoeboid-like patch, with indistinct margins, extending temporally to the fovea	ICG: peripapillary lesions appeared hypofluorescent 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 FAF: multiple hypoautofluorescent peripapillary lesions, corresponding to the older atrophic lesions, and a serpiginous-like patch of hyper-autofluorescence approaching the foveal region	Early follow-up period: the described active lesion LE started to fade, and VA LE improved to 20/100
Sanjay et al. (2021) [41]	1	42 y; F	12 d	BOV	Central serous retinopathy	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	OCT: reduction of the subretinal fluid and the hyper-reflective material and resolution of the PED
Sharma et al. (2021) [42]	1	22 y; F	14 d	BOV in the inferior field	Optic disc edema (parainfectious optic neuritis) and retinal vessel tortuosity	HFA: inferior field 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	Subjective resolution of scotoma following treatment

: 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, relative afferent pupillary defect; VL, vision loss; CRAO, central retinal artery occlusion; AMN, acute macular neuroretinopathy; HFL, henle fiber layer; ONL, outer nuclear layer; EZ, ellipsoid; IZ, interdigitation zones; DCP, deep capillary plexus; SRF, Subretinal fluid; CRVO, central retinal vein occlusion; AV, arteriovenous; FAF, fundus autofluoroscence; CME, cystoid macular edema; NSD, neurosensory detachment; SMD, serous macular detachment; VA, visual acuity; ICG, indocyanine green angiography; PED, pigment epithelial detachment.

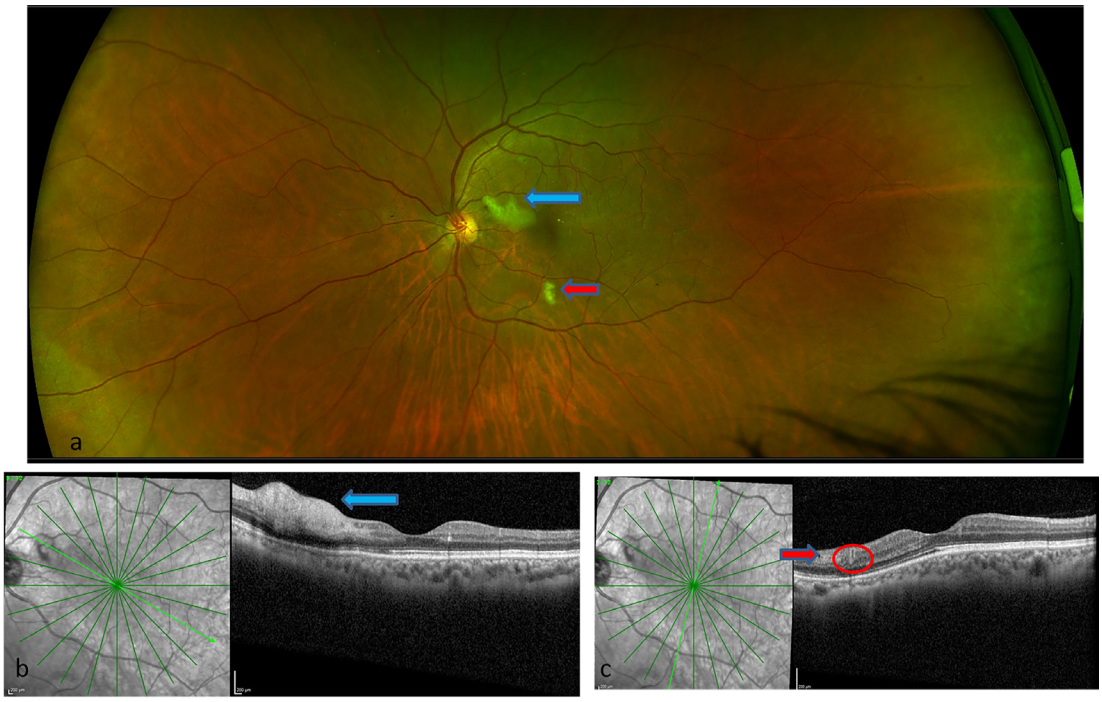

Figure 2. A 51-year-old Asian Indian female presented with blurring of central vision of 2 weeks' duration. She had been tested for COVID-19 on two previous occasions in the last 6 months and was SARS-CoV-2-negative by reverse-transcription polymerase chain reaction. She was known to have diabetes, with mild diabetic retinopathy in both eyes, and her condition was stable. (A) At this episode she had a retinitis patch temporal to the optic disc of the left eye (blue arrow) and a cotton wool spot (CWS) at the inferior macula (red arrow). (B) Corresponding spectral-domain optical coherence tomography (SD-OCT) over the retinitis patch showed disorganization and swelling of the inner and middle retinal layers (blue arrow). (C) Over the CWS, SD-OCT showed focal swelling of the nerve fiber layer (red arrow). The red circle indicates a blood vessel. The only positive result was an increased high SARS-CoV-2 IgM/IgG total antibody titer. The inflammatory markers, the erythrocyte sedimentation rate and C-reactive protein levels, were within normal limits.

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 Purtschner-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 Purtschner-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

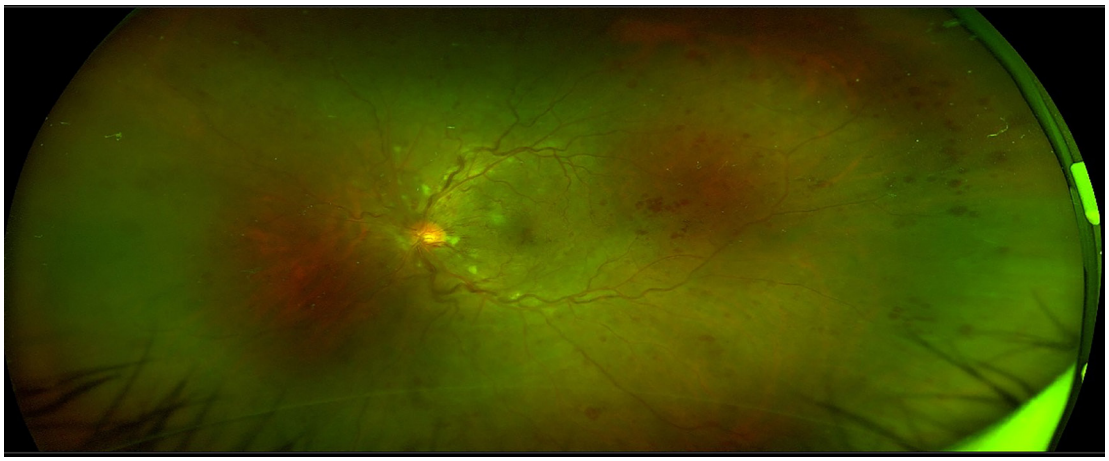

Figure 3. A 56-year-old Asian Indian male, who had no known systemic disease history, presented with blurring of vision in his left eye. On evaluation, he was diagnosed to have central retinal vein occlusion with macular edema, with poor vision (20/200) in the left eye. On investigation, his erythrocyte sedimentation rate was elevated, he had hyperhomocysteinemia (detected during the investigations). His carotid Doppler and lipid profile were normal. He had a high SARS-CoV-2 IgM/IgG total antibody titer.

(CRVO) has been reported in four cases [30-33] 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]. Turker 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 choriocapillary 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

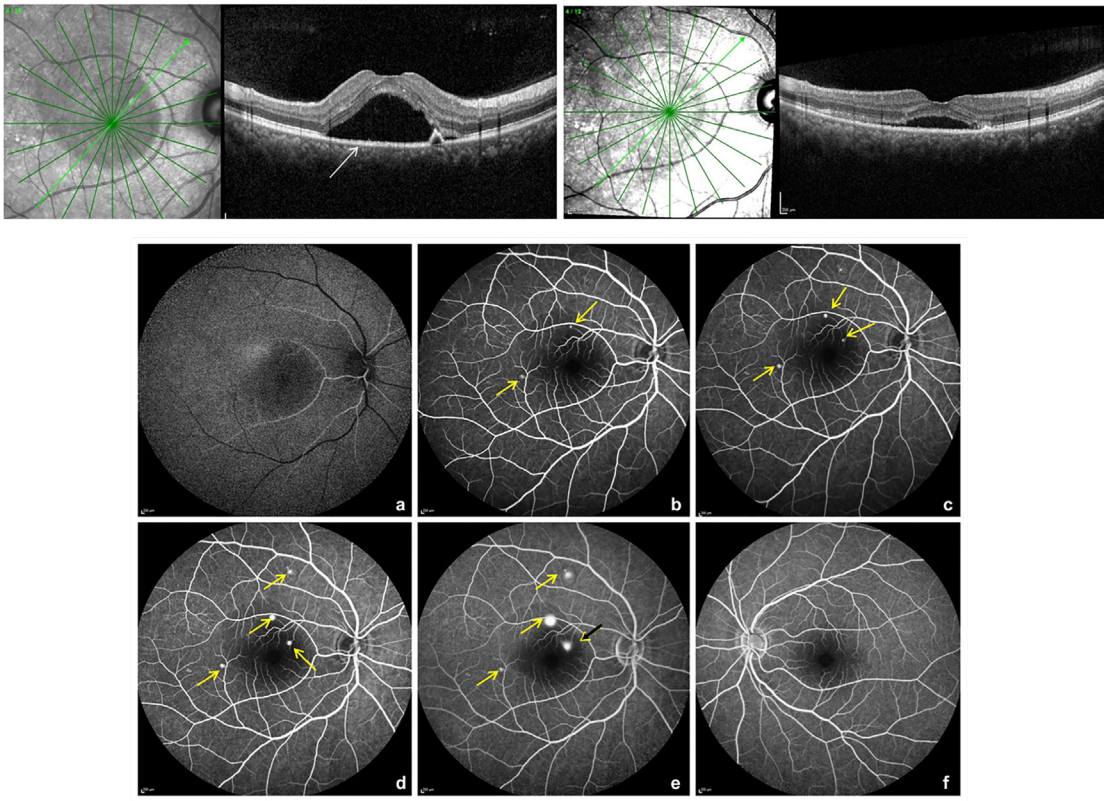

Figure 4. Spectral-domain optical coherence tomography images showing the presence of right eye subretinal fluid with pigment epithelial detachment after being treated for COVID-19 infection (upper left). Once steroids were stopped, the serous fluid reduced 1 month later (upper right). (A-E) Fundus fluorescein angiography of the right eye from the early phases (A, B) to later phases (C-E). The yellow arrows point to an initial pinpoint leak that increased in size in later phases, resembling an ink-blot pattern. The black arrow with yellow arrow-head adjacent to the optic disc shows a mixed ink-blot and fine smoke-stack pattern. (F) The normal left eye. This figure has been reused from J Ophthal Inflamm Infect, a journal from Springer Nature, with permission under Creative Commons Attribution v4.0 International license (CC BY). [41]

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.

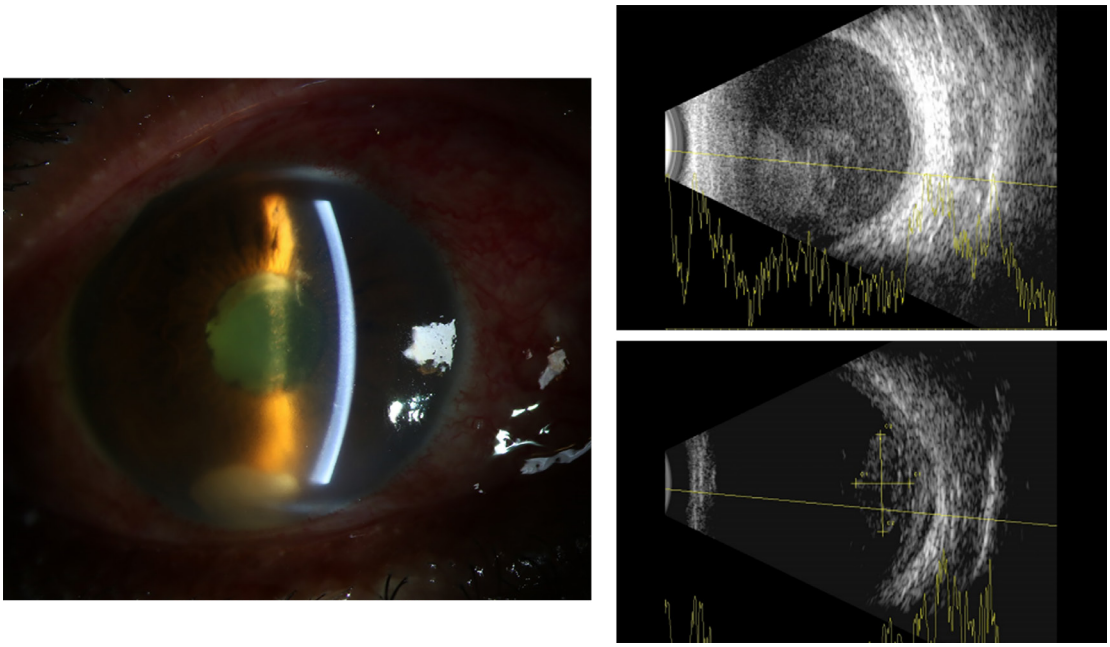

Figure 5. A 47-year-old Indian male, who was COVID-19-positive with no other systemic illness, developed right eye visual blurring 3 weeks after COVID-19 diagnosis and was diagnosed as having endogenous endophthalmitis. The diffuse slit lamp image of the right eye (figure on the left) shows ciliary congestion, 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

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