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POST-COVID-19 SYNDROME: EYE POSTERIOR SEGMENT PATHOLOGIES (LITERATURE REVIEW)

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Abstract:

Coronavirus disease (COVID – 19) was one of the most severe pandemics that the world has ever seen. The infection ranges from asymptomatic, mild to life threatening respiratory distress. It can affect almost every organ of the body, including the organ of vision. Ophthalmic manifestations may be present in the course of COVID-19 infection or they may develop later in rehabilitation period. The aim of the research is to facilitate the diagnostics and initiation of comprehensive therapy of pathological eye conditions of posterior segment of eyes that occur in coronavirus disease.

Keywords: organ,respiratory distress

The coronavirus global pandemic has caused significant negative effect on lives of millions with diversity of clinical features and life and sight – threatening consequences. The full spectrum of the disease is yet to be unraveled. We believe it is important for ophthalmologists to have knowledge about the ophthalmic manifestations of the novel viral infection in order to suspect, diagnose, refer and treat the conditions with skills, machinery, and drugs that we already possess. This article gives an overview of the ophthalmic conditions that have been associated with the virus, directly or indirectly.

METHODS

Literature research has been made in PubMed for 'COVID-19 Posterior segment pathologies'. Articles in the English language, published between January 1, 2020 to January 31, 2020, were studied, analyzed and presented in the given article.

Posterior Segment pathologies

Posterior segment involvement has varied manifestation and are actually vascular, inflammatory, and neuronal changes triggered by the viral infection but not specific to COVID-19.

RETINAL VASCULAR OCCLUSIONS

Central retinal vein occlusion (CRVO)

CRVO is one of the many vascular manifestations of COVID-19. In the published reports, only one patient suffered from hypertension and morbid obesity. It is not possible to correlate the development with the severity of COVID-19 disease. Investigations in these cases, like fluorescein angiography (FA) and optical coherence tomography (OCT) demonstrate features not different from CRVO from non-COVID-19-related causes. [Fig. 1] Patients of COVID-19 are in a procoagulant state evident by elevated D-dimer, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and cytokines even in the absence of common systemic conditions like hypertension, diabetes or dyslipidemia. Additionally, intermittent hypoxia in patients with pneumonia can induce the endothelial cells to release tissue factor and trigger the extrinsic coagulation cascade. In the impending stage, high dose steroids may help to normalize the inflammatory markers and coagulation indices. Management is with anti-vascular endothelial growth factor (anti-VEGF) in the established phase.[1,2,3,4] In patients with systemic comorbidities with severe COVID-19 infection, early anticoagulant prophylaxis should be considered.

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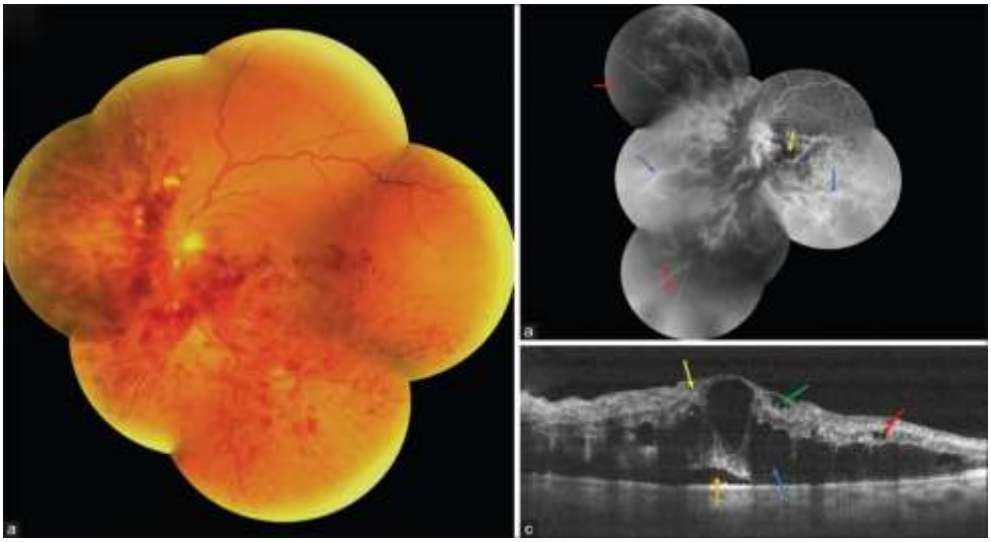

Figure 1. Vasculitic retinal vein occlusion as a manifestation of COVID-19: A 52-year-old patient presented with the diminution of vision in the left eye 10 days after he tested positive for SARS-CoV-2. (a) Fundus photograph demonstrating inferior hemiretinal vein occlusion with superonasal branch retinal vein occlusion. (b) Fundus fluorescein angiogram showing the presence of dilated tortuous vein in inferior and superonasal quadrants with late phases showing staining and leakage from the vessel walls (Blue arrow), multiple areas of hypofluorescence corresponding to retinal hemorrhages clinically, suggestive of blocked fluorescence (Yellow arrow) and areas of hypofluorescence suggestive of capillary nonperfusion (Blue arrow) in involved quadrants. The macular region and optic disc also showed hyperfluorescence in late phases suggestive of leakage. (c) Spectral domain optical coherence tomography illustrating the presence of serous macular detachment (Orange arrow), cystoid macular edema, cysts located in outer nuclear layer (Blue arrow), inner nuclear layer (Red arrow) and ganglion cell layer (Green arrow) and disorganization of retinal inner layers (Yellow arrow) (Reproduced with permission from Sheth JU, Narayanan R, Goyal J, Goyal V. Retinal vein occlusion in COVID-19: A novel entity. Ind J Ophthalmol 2020;68:2291-3).

Central retinal artery occlusion (CRAO)

Sudden onset of painless vision loss can herald the occlusion of central retinal artery with grave visual prognosis. Both patients, in the reported cases, had elevated inflammatory markers including IL-6, CRP, ferritin, fibrinogen and D-dimer as a result of severe COVID-19 infection, possibly resulting in the vascular occlusion.[5,6] In the case reported by Dumitrascu *et al.*, incomplete ophthalmic artery occlusion developed despite the patient being on enoxaparin for deep vein thrombosis.[7] Combined retinal vein and artery occlusion has also been seen (unpublished) in a patient following COVID-19 infection[Fig.2].

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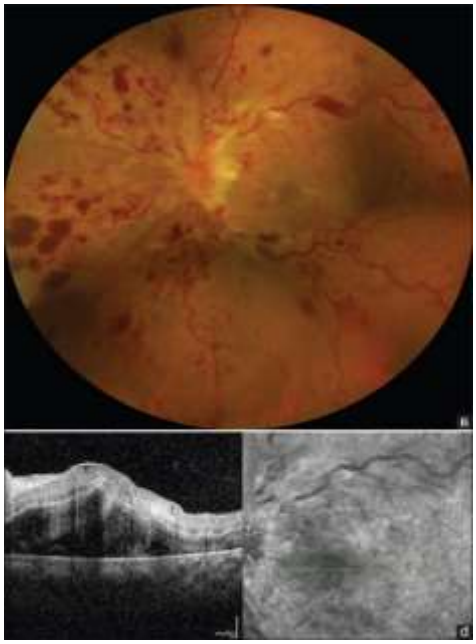

Figure 2. Combined central retinal artery and vein occlusion following COVID-19: A 32-year-old lady, known hypertensive with past history of COVID-19, presented with sudden onset, painless diminution of vision in the right eye. Examination showed right eye visual acuity of finger counting at 50cm and RAPD. (a) Fundus photograph showing retinal hemorrhages in all quadrants, dilated tortuous vessels and optic disc edema. (b) SD-OCT showing neurosensory detachment with intraretinal fluid and hyper-reflectivity of inner retinal layers. (Contributed by Rajashree Salvi and Shrinivas Joshi, M M Joshi Eye Institute, Hubli, India)

Acute macular neuroretinopathy (AMN), paracentral acute middle maculopathy (PAMM)

AMN is a rare condition with unknown etiology but, about 50% have been shown to be associated with respiratory or influenza-like illness. Ischemic mechanism involving the deep capillary plexus has been proposed. Cases of AMN and PAMM have been reported following/concurrently with COVID-19 diagnosis.[8,9,10] In a yet unpublished report from India, a 28-year-old healthy woman was diagnosed with AMN 1 week after recovery from mild COVID-19 infection. [Fig. 3] In the case reported by Zamani *et al.* from Iran, the patient was recently diagnosed with acute myeloid leukemia (AML) and was on chemotherapy. It is difficult to conclude with certainty if the retinal findings in this case were a manifestation of AML or if the viral infection predisposed the patient to AMN.[11] Acute painless diminution of vision, faintly colorful paracentral scotoma, and dyschromatopsia are the common symptoms. Fundus examination may not reveal any obvious abnormality, although retinal hemorrhages with Roth spots and a wedge-shaped reddish-brown lesion directed towards fovea have been described. Spectral-domain OCT (SD-OCT) is invaluable in detecting hyperreflectivity at the level of outer plexiform layer (OPL), outer nuclear layer (ONL) or between outer plexiform layer (OPL) and inner nuclear layer (INL). Disruption of ellipsoid zone (EZ), interdigitation zone (IZ), and loss of INL volume have also been described [Fig. 4]. OCT-angiography (OCT-A) in PAMM shows reduced flow in intermediate, deep and superficial capillary plexus, and in AMN, there is reduced flow in the deep plexus.

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Fig.3

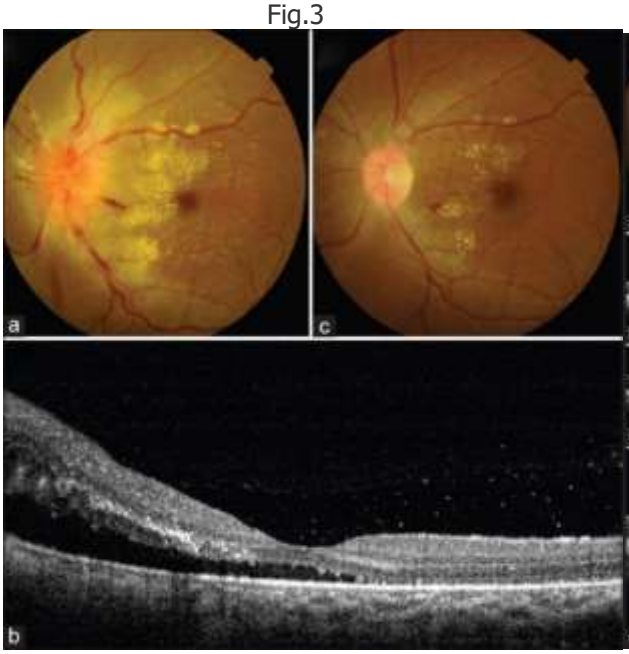

Fig.4

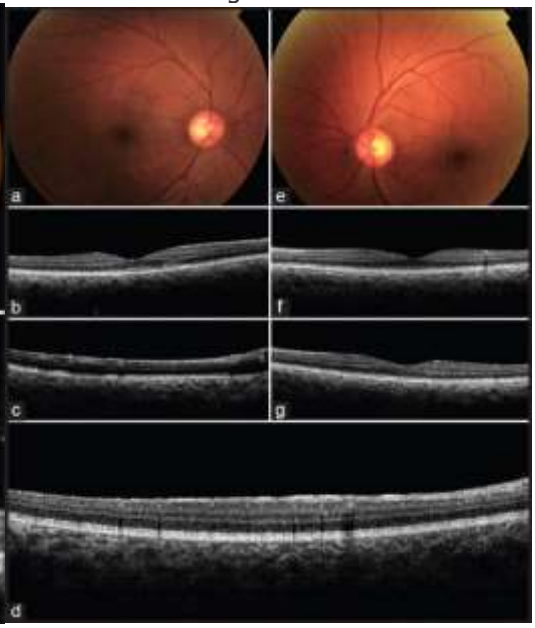

Figure 3. Acute macular neuroretinopathy following COVID-19: A 28-year-old woman presented with diminution of vision in left eye seven days after recovering from a mild COVID-19 infection. Vision was 6/36 in left eye with RAPD. (a) Fundus examination showed vitritis 1+, blurred disc margins, hard exudates over macular area and internal limiting membrane folds. (b) SD-OCT showed neurosensory detachment and outer retinal hyperreflective foci. She was managed with tapering doses of oral steroids and topical steroid and homatropine. (c) After 1 month, vision had recovered, disc edema had subsided with resolving exudates. (Contributed by Debdulal Chakraborty, Vitreoretina Services, Disha Eye Hospitals, Kolkata, India

Figure 4. Acute macular neuroretinitis (AMN) and paracentral acute middle maculopathy (PAMM) as a manifestation of COVID-19: A 32-yearold male presented with abrupt onset paracentral triangular negative scotoma in his right eye noted below and to the right side of the centre of his visual field. History was significant for recovery from COVID-19 infection recently. Left eye was asymptomatic. (a) Fundus evaluation of the right eye revealed a triangular greyish-white lesion in deeper retina superonasal to the macular centre. (b) Optical coherence tomography (OCT) revealed corresponding areas of disruption in the outer retinal layers in addition to (c) other hyper-reflective lesions in more superficial retinal layers causing shadowing in underlying deeper retina. (d)There was hyper-reflectivity of the entire inner retinal surface just inferior to foveal centre. (e)Left eye fundus examination revealed a small whitish lesion nasal to foveal centre and multiple smaller lesions inferonasal and temporal to centre; (e) OCT revealed a single hyper-reflective lesion in the superficial retina with shadowing temporal to centre and (g) hyperreflectivity of the entire inner retinal surface nasal to centre. These findings suggested post-COVID-19 right eye symptomatic AMN and bilateral asymptomatic PAMM. (Contributed by Mallika Goyal, Retina-Vitreous Service, Apollo Eye Institute, Apollo Hospitals, Hyderabad, India)

RETINA

Vitritis and outer retinal abnormalities

The presenting complaint in this case was bilateral redness in eyes. SD-OCT showed hyperreflectivity at the level of posterior vitreous hyaloid corresponding to the vitritis. Hyperreflectivity was also present at the level of inner plexiform layer (IPL), ganglion cell layer (GCL) with disruption of EZ. FA showed corresponding hyperfluorescence. It is important to rule out other infectious causes of vitritis like HSV, cytomegalovirus (CMV), syphilis, bartonella, toxoplasma, borrelia, toxocara, and inflammatory diseases which can cause uveitis. In the absence of any of these, COVID-19 was presumed to have led to the development of abnormalities detected on OCT.[12]

Acute retinal necrosis (ARN)

The reported patient was immunocompromised with relapsed diffuse large B cell lymphoma and had completed chemotherapy two months ago. A known case of systemic lupus erythematosus (SLE), she

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presented with ocular complaints of floaters and reduced vision. Intravitreal specimen tested positive for varicella-zoster virus (VZV) but not for COVID-19.[13] ARN is not common in immunosuppressed states, neither is the amount of inflammation seen in this patient which led to the presumption that COVID-19 had a role to play in triggering the VZV-related ARN by its effect on the immune system. It is possible that SARS-CoV-2 may compromise the blood-retinal barrier allowing a heightened inflammatory response.

Other retinal findings seen in patients with COVID-19

Pereira *et al.*, from Brazil, reported retinal findings in patients admitted with severe COVID-19. The cross-sectional study showed retinal changes in ten patients (55.6%) and included peripheral retinal hemorrhages, macular hyperpigmentation, retinal sectoral pallor, peripapillary flame-shaped hemorrhages, hard exudates, and cotton wool spots. All the patients were on prophylactic or full intensity anticoagulants to counter the prothrombotic condition in severe cases of COVID-19. But the superadded or primary effect of pre-existing comorbidities, ICU admission, and vasoactive pharmacological support was not taken into account. The retinal findings, thus, cannot be solely attributed to the viral infection.[13]

UVEA

Serpiginous choroiditis

Reactivation of serpiginous choroiditis following COVID-19 infection was reported by Providencia *et al.* This patient had older pictures of prior retinal examination which showed evidence of atrophic lesions on FA indicative of previous episode of choroiditis.[14] There are unpublished cases of multifocal or serpiginous choroiditis presenting in patients with a history of SARS-CoV-2 infection. It is difficult to determine whether these are new onset or reactivation of inflammation. Autoimmunity activated by SARS-CoV-2 is believed to play a role in this. Tests for tuberculosis (TB), Hepatitis B and C (HBV, HCV), human immunodeficiency virus (HIV), borrelia, and syphilis should be done to diagnose serpiginous like choroiditis and before starting immunomodulatory therapy.[15]

SARS-CoV-2 RNA has been detected in the retina of patients diagnosed with COVID-19 in a study by Casagrande *et al.* in Germany. Three of the fourteen eyes enucleated on autopsy showed the presence of all three gene sequences on RT-PCR- RdRp-gene, E-gene, Orfl. The authors rightly state that the actual rate of RNA detection in retina may be much more because it depends on the post-mortem interval for the collection of the specimen, the Ct values and the biopsy size.[16] In animal models, retinitis and uveitis have been shown to develop. Angiotensin converting enzyme 2 (ACE-2) receptors have been detected in the retina. But none of the studies have answered the question of viral replication within ocular structures. Many of the manifestations are a result of predisposition to arterial and venous thrombosis in patients with the novel coronavirus infection. Cavalcanti *et al.* reported three patients, younger than 41 years with cerebral venous thrombosis.[17] Pulmonary embolism, stroke, disseminated intravascular coagulation (DIC), limb, and digit infarcts are also seen in these patients. Venous thromboembolism is seen in as many as 19-25% of the COVID-19 patients in ICU and on anticoagulants. Thus, development of retinal venous or arterial occlusion is not surprising. But what is surprising is, their development even in patients with mild to moderate symptoms.[18,19] It can develop within a few days to almost three weeks after the onset of COVID-19 symptoms. Patients presenting with CRVO to an ophthalmologist could have undiagnosed active or past infection with COVID-19. In the panel of investigations for a patient with retinal vascular occlusion, COVID-19 should now find a place. In the absence of comorbidities and in young adults, vasculitis can produce retinal vascular occlusion. The delayed onset can be explained by the immune complex deposition as a part of type 3 hypersensitivity reaction producing a pro-inflammatory state with cytokine storm. This is similar to the pathogenesis of vasculitis in other viral infections like chikungunya and dengue and systemic vasculitis.

In a correspondence, Marinho *et al.* in May 2020 discussed about retinal findings on OCT in 12 patients with COVID-19. All patients showed hyperreflective lesion at GCL and IPL prominently at the papillomacular bundle. The affinity for ganglion cells and plexiform layer may explain the associated central nervous system (CNS) manifestations as well.[20] In a case-control study from Spain, COVID-19 patients with moderate to severe disease had consistently decreased central vascular density on OCT-A as compared to patients with mild disease or controls without the viral infection. The immune cells recruited by the virus in the vessel walls are believed to produce endothelial cellular edema. Indirectly, the viral infection can induce an immune response with endothelial dysfunction associated with apoptosis. Central vascular density is considered a biomarker for several diseases like diabetes, chronic kidney disease, inflammatory bowel disease and Alzheimer's and has a potential to become a biomarker for microvascular damage in COVID-19 patients, though larger, population-based studies are essential.[21]

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CONCLUSION

The prevalence of ophthalmic manifestations among COVID-19 patients ranges from 2-32%.[22]. The given complications certainly deteriorate the life quality of individuals with COVID-19 infection. Thus it is crucial for eye-care specialists to get familiarized with the data provided in fresh researches carried out worldwide as well as in the given literature review and to be able to recognize and address them with sophisticated knowledge.

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