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Brief report

COVID-19 and ocular manifestations – benign to fatal

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The SARS Cov-19 (COVID-19) pandemic has hit the world with long-lasting consequences. The full spectrum of the disease and resulting complications are yet to be unveiled. The permanent sequelae to different organ systems, the multitude of presentations, the theories of pathogenesis, and the associations with COVID-19 infection studied and reported continuously with ever-changing evidence.

COVID-19 first reported in Wuhan in China in December 2019, spread to all parts of the world to the proportion of a pandemic by March 2020. The illness can range from asymptomatic or mild flu-like symptoms to severe acute respiratory distress and death. Apart from the respiratory system, it can damage all body organs, including blood, cardiovascular, neurological, and gastrointestinal systems.

An ophthalmologist was the first to report the virus in Wuhan, China, and himself contracted and succumbed to the disease while treating a patient for glaucoma. Ophthalmic manifestations vary in presentation, severity, and timing and could be the presenting feature. Ophthalmic manifestations are more common in patients with a severe systemic disease with abnormal blood and inflammatory parameters[1,2].

Exposure of unprotected eyes can lead to infection with COVID-19 virus[3]. Routes of the transmission of the virus to the eyes include direct inoculation of conjunctiva by droplets, migration of upper respiratory tract infection through the nasolacrimal duct, or lacrimal gland involvement by the hematogenous route[4].

There is no evidence of viral replication in ocular tissues[4,2]. But it is advisable and safer to use universal precautions, goggles, slit lamp breath shields, and sanitization techniques by ophthalmologists while examining patients or suspected patients with COVID-19.

Ophthalmic manifestations

The ophthalmic manifestations can develop at any point in the disease course and follows a timeframe. The prevalence of ophthalmic manifestations among COVID-19 patients ranges from 2 to 32%[5]. Knowledge of this timeframe is vital to ophthalmologists to look for specific features depending on the stage of the disease. The median time of appearance of neuro-ophthalmic features is five days, for ocular surface and anterior segment manifestations are 8.5 days, and posterior segment and orbital pathology is 12 days. Ocular manifestations are more common in patients with severe disease and with higher white blood cell (WBC) count, C-reactive protein, procalcitonin, and lactate dehydrogenase levels[2].

Eyelid involvements

Eyelid manifestations in the form of meibomian orifice abnormalities and lid margin hyperaemia or telangiectasia were found in 38% of patients in one study in Italy[6]. It may develop as late manifestation of the disease, and the incidence is also expected to rise in the post-pandemic era.

Conjunctival manifestations

The conjunctival findings were significantly correlated with the severity of the disease rather than the duration of the disease and range from follicular conjunctivitis to haemorrhagic and pseudomembranous conjunctivitis.

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Ocular surface manifestations of COVID-19 can be acute (within a week) or delayed (after a week). Although diffuse follicular conjunctivitis may be found in both forms, an immune response is considered to play a significant role in the delayed development of signs[7]. Conjunctival congestion may be an early sign of COVID-19 infection even before the development of systemic symptoms[8]. The recurrent and delayed cases had more severe forms of the disease than isolated acute conjunctivitis[7]. Conjunctivitis was the presenting feature and the sole manifestation of COVID-19 infection in some cases[9,10]. Treatment involves mainly lubricants, and the disease is self-limiting. Topical antibiotics may be added to prevent bacterial superinfection. Ribavirin has been used in some cases[5]. Topical steroids have a role in immune-mediated keratoconjunctivitis and episcleritis. Long-term sequelae are unknown at present.

One should have a high index of suspicion for COVID-19 in patients presenting with conjunctivitis. Patients with conjunctivitis should be specifically asked for COVID-19 related symptoms and advised to get tested if present. Further studies are necessary to determine if the conjunctiva can be a portal of entry and reservoir of the virus.

Follicular conjunctivitis is the most common ophthalmic manifestation documented in COVID-19 patients. All symptomatic patients gave a history of redness of one or both eyes[6]. The manifestations are more common in the middle phase of the disease[5]. Conjunctivitis responds to lubricants and preservative-free moxifloxacin eye drops. The virus shedding in the conjunctiva may persist even after the nasopharyngeal swab becomes negative for the virus[11]. Kerato-conjunctivitis was the initial presentation in some patients with mild respiratory symptoms[12]. Haemorrhagic and pseudomembranous conjunctivitis had been reported in a patient with severe COVID-19 infection, 19 days after the onset of systemic symptoms. Treatment was with azithromycin and dexamethasone drops and daily debridement of the pseudomembrane[13].

Conjunctivitis in children

A 30-fold increase in the incidence of Kawasaki disease-like condition has been reported in children in some parts of Italy with a strong association with COVID-19. This atypical presentation is known as a multisystem inflammatory syndrome in children (MIS-C)[14]. Kawasaki disease, a form of self-limiting vasculitis, is associated with iridocyclitis, punctate keratitis, vitreous opacities, papilloedema, subconjunctival haemorrhage, and conjunctival injection[15]. The main ophthalmic manifestation was conjunctivitis[14]. MIS-C is commonly being noted to have serological positivity for COVID-19 than on nasopharyngeal swab, indicating it to be a manifestation of delayed immunological response to COVID-19. Treatment is directed towards suppressing systemic inflammation. Corticosteroids, intravenous immunoglobulin (IVIG), and aspirin have been used in the cases reported[14,2].

Episcleritis

Most cases of episcleritis are idiopathic and self-limiting[6,2].

Posterior segment manifestations

Posterior segment vascular, inflammatory, and neuronal changes are not specific to COVID-19. The median duration between the appearance of ophthalmic symptoms and the COVID-19 symptoms and diagnosis was 12 (17.6 ± 13.1, 4-55) days[2].

Retinal vascular occlusions

Many of the manifestations are a result of predisposition to arterial and venous thrombosis in patients with the novel coronavirus infection. Patients with mild to moderate symptoms are even predisposed to thrombosis[16,17]. It can develop within a few days to almost three weeks after the onset of COVID-19 symptoms. Patients presenting with vascular occlusions to an ophthalmologist could have an undiagnosed active or past infection with COVID-19. 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. Retinal findings on OCT have shown hyperreflective lesion at ganglion cell layer (GCL) and inner plexiform layer (IPL) prominently at the papillomacular bundle. The affinity for ganglion cells and plexiform layer may explain the associated central nervous system manifestations as well[12].

Central retinal vein occlusion (CRVO)

CRVO is one of the many vascular manifestations of COVID-19. Features are not different from CRVO from non-COVID-19 related causes. 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 dyslipidaemia. Inter-

mittent hypoxia with pneumonia can induce the endothelial cells to release tissue factors 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[18,19,20,21]. In patients with systemic comorbidities with severe COVID-19 infection, early anticoagulant prophylaxis should be considered.

Central retinal artery occlusion (CRAO)

Occlusion of the central retinal artery has a grave visual prognosis. 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 vascular occlusion[22,23].

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

AMN is a rare condition with unknown aetiology, but about 50% have been shown to be associated with respiratory or influenza-like illness. The ischemic mechanism involving the deep capillary plexus has been proposed. Cases of AMN and PAMM have been reported following and concurrently with COVID-19[24,25,26]. Acute painless diminution of vision, faintly colourful paracentral scotoma, and dyschromatopsia are the common symptoms. Fundus examination may not reveal any obvious abnormality, although retinal haemorrhages 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 the outer plexiform layer (OPL), outer nuclear layer (ONL), or between the outer plexiform layer (OPL) and inner nuclear layer (INL). Disruption of the ellipsoid zone (EZ), interdigitation zone (IZ), and loss of INL volume have also been described. 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[2].

Retinal manifestations

Vitritis and outer retinal abnormalities have been documented in the literature. The presenting complaint, in these cases, was bilateral redness in the eyes. SD-OCT showed hyperreflectivity at the level of posterior vitreous hyaloid corresponding to the vitritis. Hyperreflectivity was also present at the level of the inner plexiform layer (IPL) and ganglion cell layer (GCL) with disruption of EZ. Fluorescein angiography (FA) showed the corresponding hyperfluorescence[27].

Acute retinal necrosis (ARN), peripheral retinal haemorrhages, macular hyperpigmentation, retinal sectoral pallor, peripapillary flame-shaped haemorrhages, hard exudates, and cotton wool spots, reactivation of serpiginous choroiditis all are reported following COVID-19 with COVID-19[28,29,30].

Neuro-ophthalmic manifestations

Papillophlebitis is an uncommon condition seen in healthy, young adults has been reported in COVID-19 patients also. It results in a painless, unilateral, slight diminution of vision. Visual fields show an enlarged blind spot. Ophthalmic findings include dilated, tortuous retinal vessels, disc oedema, superficial retinal haemorrhages, cotton wool spot with or without macular oedema. Fluorescein angiography shows discrete venous staining and leakage late staining of the optic disc but no evidence of ischemia or peripheral vasculitis. The final visual prognosis is quite favourable. About 30% of the cases develop vision-threatening ischemic venous occlusion with consequent neovascular glaucoma and macular oedema. The role of COVID-19 as a possible cause comes in view of its association with coagulopathy and disproportionate inflammatory response and cytokine storm[31]. Bilateral optic neuritis was reported within a week after COVID-19 symptoms[32]. Adie's tonic pupil, Miller Fisher Syndrome (MFS), neurogenic ptosis and delayed onset of ocular myasthenia gravis have also been reported with COVID-19[33]. MFS with acute onset ataxia, loss of tendon reflexes, and ophthalmoplegia and cases of cranial nerve palsies have been reported in several patients with COVID-19. Patients gave a history of acute onset of diplopia as the ocular complaint. Abducent nerve was most involved followed by oculomotor nerve. Good response to immunoglobulin supports the immune-mediated pathogenesis[34,35,36,37,38,39].

Cerebrovascular accident (CVA) with vision loss

Acute vision loss following CVA can also result from the procoagulant state in COVID-19 infection. Pre-existing endothelial dysfunction may make patients more susceptible. Acute onset of bilateral, painless vision loss should prompt the treating physicians to advise an urgent imaging of the brain with circle of Willis angiography[40].

Based on the above findings, it is important that physicians ask leading questions about double vision, decreased vision, pain with eye movements, gait abnormalities, or other neurological conditions in patients with COVID-19. COVID-19 testing is

mandatory in patients presenting with these complaints, while advising other tests to determine the aetiology, in the current context.

COVID-19 treating medical team should also do a quick assessment of visual acuity, pupillary response, ocular motility, ptosis, optic disc, and reflexes daily since majority of these conditions occur in the early phase of the disease.

Orbital manifestations of COVID-19

The orbital manifestations of COVID-19 can vary from intense retro-orbital pain to life-threatening invasive mucormycosis. Orbital emphysema is a complication in intubated patients receiving positive end expiratory pressure ventilation. As with other ophthalmic manifestations, direct effect of the virus, altered immune status, proinflammatory milieu and escalated coagulative profile play variable role in the pathogenesis.

Dacryoadenitis and orbital cellulitis and sinusitis are documented complications of COVID-19[41,42]. In the initial stages of the disease, the virus can travel to the lacrimal gland via the lacrimal ductules or by direct hematogenous spread. Later, immunological response incited by the virus may affect the lacrimal gland producing inflammation. Acute dacryoadenitis responds well to systemic steroids. COVID-19 induced upper respiratory congestion can compromise mucociliary clearance with secondary sinus obstruction and bacterial infection. Children have a indolent course with 56% of them being asymptomatic or having mild symptoms[43].

Mucormycosis

Mucormycosis is a life-threatening, opportunistic infection and patients with moderate to severe COVID-19 are more susceptible to it because of the compromised immune system with decreased CD4+ and CD8+ lymphocytes and comorbidities such as diabetes mellitus, decompensated pulmonary functions, and the use of immunosuppressive therapy (corticosteroids). Mortality rate is as high as 50% even with treatment[44,45,46].

Almost 70% of rhino-orbital-cerebral mucormycosis is seen in patients with uncontrolled diabetes and most of them have ketoacidosis at the time of presentation. The symptoms of rhino-orbital mucormycosis developed as late as 30-42 days after the diagnosis of COVID-19. High index of suspicion, early diagnosis with histopathological and microbiological evidence, appropriate management with antifungals and aggressive surgical debridement (functional endoscopic sinus surgery and orbital exenteration) can improve survival. A nasal swab for KOH mount and culture is a bedside procedure. Orbital exenteration for life-threatening infection is triaged as an urgent condition requiring surgery within 4-72 hours. Intravenous liposomal amphotericin B should be started based on clinical suspicion or results of deep nasal swab. MRI is useful to determine the extent of the disease and intra-cranial extension. Patients should also be made aware about the risks involved with the treatment of COVID-19 and the need for strict glycaemic control. Development of unilateral facial or orbital pain, headache, periocular swelling or double vision or diminution of vision should prompt even the COVID-19 recovered patients to seek immediate medical attention[2]. Since majority of the patients developed symptoms of mucormycosis after recovering from COVID-19, it is important to follow-up of high-risk COVID-19 patients[2,47].

Orbital histiocytic lesion

A benign histiocytic proliferative lesion presenting as an orbital mass and lymphadenopathy, suggestive of a Rosai-Dorfman disease was documented in an elderly individual presenting six months after COVID-19, suggest that the virus may have a role on the immune system of the body[48].

Drug induced ocular toxicity

The medications that have been used to treat COVID-19 also have ocular toxicities. Chloroquine and hydroxychloroquine can lead to retinal toxicity, but it is not expected or seen with the brief period of use for COVID-19. Lopinavir and Ritonavir are known to results in reactivation of autoimmune conditions. Ribavirin is known to cause retinopathy, retinal vein occlusion, serous retinal detachment, non-arteritic ischemic optic neuropathy and Vogt-Koyanagi-Harada (VKH) disease.

Side effects of interferon include retinopathy, VKH, conjunctivitis, uveitis, optic neuropathy, corneal ulcers, epithelial defects, and Sjogren's syndrome. Tocilizumab has been reported to produce cotton wool spots and retinal haemorrhages. Systemic corticosteroids therapy is associated with glaucoma and central serous chorioretinopathy. Central retinal vein occlusion was reported in patients receiving IVIG[2,49].

Conclusion

COVID-19 is not a just a viral infection affecting a one system. Benign and life-threatening ocular manifestations should be diagnosed promptly and treated appropriately to save the vision and the life. The importance of strict glycaemic control in diabetic patient is mandatory to prevent life threatening ocular complications.

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