Introduction

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had health implications of unprecedented magnitude. The COVID-19 illness can range from asymptomatic or mild flu-like symptoms to severe respiratory distress. It is now known that it can have effects on almost all organs of the body including the cardiovascular, neurological and gastrointestinal systems. Ophthalmic manifestations are varied in terms of presentation, severity and timing. While conjunctivitis is the most common ocular condition seen in COVID-19 patients, other pathologies described in association with the SARS-CoV-2 infection include keratoconjunctivitis, episcleritis, blepharitis, retinal vein or artery occlusions, acute macular neuroretinopathy, paracentral acute middle maculopathy, vitritis, outer retinal abnormalities and reactivation of varicella zoster induced acute retinal necrosis and serpiginous choroiditis. Neuro-ophtalmic complications that have been reported include papillophlebitis, optic neuritis, Adie's tonic pupil, Miller Fisher syndrome, cranial nerve palsies, neurogenic ptosis and acute vision loss following cerebrovascular accident. Orbital manifestations are uncommon and there are only a few isolated case reports. 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. Here we present a brief review of the published literature on orbital pathologies seen in patients with COVID-19 infection.

There are not many orbital manifestations described but it is expected that their incidence will rise considering the interplay of comorbidities and treatment along with the infection itself. The case reports and series published show patients with a mean age of 50.2+/-43 (median 60, 12-76) years. 12/14 patients were males with nine being diabetics and six hypertensive patients. Asthma was notably present in eight patients. Five of these patients presented either with ophthalmic symptoms and were tested for COVID-19 on screening or presented concurrently with systemic symptoms of viral infection. The mean time of presentation from the development of COVID-19 symptoms was 15.8+/-13.8 (median 12,2-42) days. 10/14 patients had moderate to severe disease.

Dacryoadenitis

Dacryoadenitis is the most common cause of a painful lacrimal gland mass in a healthy young adult and the most common cause of dacryoadenitis is viral infection. In the only reported case, the patient had a four-day history of eyelid swelling and pain. The patient had history of contact with COVID-19 infected patients and his antibody tests for IgM, IgG were positive. Other tests for autoimmune conditions, infectious diseases particularly tuberculosis, mumps, adenovirus, Epstein-Barr virus (EBV), herpes simplex virus (HSV) and herpes zoster virus (HZV) were all negative. A diagnosis of acute dacryoadenitis as a late complication of SARS-CoV-2 virus was made.\(^1\) In the early 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.

Retro-orbital pain

Bilateral retro-orbital pain may be a prominent and even presenting symptom in patients with COVID-19 and can mimic conditions like dengue.\(^2\) This case highlights the important fact that COVID-19 has features which are highly non-specific and can simulate a lot of other common conditions.

Orbital cellulitis and sinusitis

In the two cases reported by Turbin et al, two adolescent boys developed acute onset unilateral, progressive,
painful orbital swelling. RT-PCR for COVID-19 was done as preoperative investigation. There were no symptoms of chronic sinus disease. Suggested mechanism is that COVID-19 induced upper respiratory congestion can compromise mucociliary clearance with secondary sinus obstruction and bacterial infection. Children have a relatively indolent course of disease with 56% of them being asymptomatic or having mild symptoms. The superior ophthalmic vein thrombosis with facial vein extension may be a thrombotic complication of SARS-CoV-2.

In another case reported by Shires et al, a 76 year old man, diabetic, hypertensive with testicular cancer and COVID-19 developed spontaneously-draining orbital abscess and globe perforation necessitating enucleation with sinus debridement. Cultures grew methicillin resistant staphylococcus aureus (MRSA), Streptococcus constellatus and Peptoniphilus indolicus with negative blood cultures. Intraoperatively, an unusual finding was a highly avascular nasal mucosa. COVID-19 may predispose a patient to infection by bacteria not known to be found in the orbit like Peptoniphilus indolicus which is present in vagina and stomach. Orbital infection with this bacteria has not been reported previously. The avascularity was most likely because of thromboembolic complications of COVID-19.

Mucormycosis

Mucormycosis is a life threatening, opportunistic infection and patients with moderate to severe COVID-19 are more susceptible to it because of compromised immune system with decreased CD4+ and CD8+ lymphocytes, associated comorbidities such as diabetes mellitus which potentiates both the conditions, decompensated pulmonary functions and the use of immunosuppressive therapy (corticosteroids) for the management. Literature shows that rhino-orbital cerebral (ROC) mucormycosis can present concurrently with COVID-19 infection in patients under treatment or diagnosed as a preoperative evaluation. Mortality rate is as high as 50% even with treatment. In the series by the authors, all, except one patient presented after recovering from COVID-19. 5/6 cases had received intravenous and/or oral steroids and all were diabetics. 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. What is interesting to note in this series is that 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 (FESS and orbital exenteration) can improve survival. The signs and symptoms of orbital mucormycosis are not different from those of mucormycosis in non-COVID-19 patients (Figure 1).

Fig.1 : Clinical picture of a 61-year-old male, who presented with (a) left periorcular edema, complete ptosis and (b) proptosis, conjunctival congestion, and severe chemosis 17 days after COVID-19 infection. He had uncontrolled diabetes mellitus and received oral and intravenous steroids as part of COVID-19 management. The patient underwent aggressive paranasal sinus debridement and was initiated on intravenous amphotericin-B, with excellent response to treatment, with eye and life salvage.
Simple tests like vision, pupil, ocular motility and sinus tenderness can be part of routine physical evaluation of a COVID-19 patient hospitalized with moderate to severe infection or diabetics with COVID-19 or those receiving systemic corticosteroids. 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. Thus, appropriate surgery has to be undertaken with full personal protective equipment. Intravenous liposomal amphotericin B is started based on clinical suspicion or results of deep nasal swab. MRI is very useful to determine the extent of the disease and intracranial extension. Patients should also be made aware about the risks involved with the treatment of COVID-19 and the need for strict glycemic control. Development of unilateral facial or orbital pain, headache, periorcular swelling or double vision or diminution of vision should prompt even the COVID-19 recovered patients to seek immediate medical attention. Since majority of the patients developed symptoms of mucormycosis after recovering from COVID-19, follow up of high risk COVID-19 patients for sequelae is imperative.

**Orbital histiocytic lesions**

The authors have seen a case (unpublished) of a 77-year-old man with bilateral proptosis, eyelid swelling, enlarged lacrimal gland, orbital mass and cervical, axillary and mediastinal lymphadenopathy and maxillary sinusitis with history of COVID-19 infection six months ago. Incisional biopsy was done and histopathology with immunohistochemistry was suggestive of a benign histiocytic proliferative lesion, possibly Rosai-Dorfman disease. This is very unusual in an elderly individual and the infection with SARS-CoV-2 may have a role in with its influence on the immune system of the body. The prevalence of ophthalmic manifestations among COVID-19 patients ranges from 2-32%. The causal relation with SARS-CoV-2 is yet to be established with certainty for any of these conditions. While the viral RNA has been identified in different parts of the eye, its replication and infectivity is not established. The transmission of the virus via eye secretions is being actively investigated. The orbital manifestations of COVID-19 can vary from intense retro-orbital pain to life threatening invasive mucormycosis. Orbital emphysema is seen as 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.

There is an imminent need for establishing evidence-based guidelines for prophylactic use of antifungals in patients with high risk of rhino-orbito-cerebral mucormycosis diagnosed with COVID-19 who require corticosteroids. As we enter the phase of vaccination, a substantial proportion of the population has already been exposed to the SARS-CoV-2 virus, either in the form of overt clinical disease or contact with a patient diagnosed with COVID-19 with subclinical illness. Several countries of the world are experiencing resurgence of cases with mutated strains.

We can expect to see more manifestations of the disease in the eye and even clusters of similar cases. Ophthalmologists should be aware of the different manifestations and keep in mind the importance of asking specific history about COVID-19 infection, contact with infected person or related symptoms. COVID-19 should be included in the lists of causes of common ophthalmic pathologies especially when there is unusual presentation of a disease in an age group or population phenotype where it is not expected like histiocytic lesion in an elderly individual. Knowledge of many of these manifestations being the presenting features can help diagnose the infection early and limit the disease transmission. Tests like nasopharyngeal swab for RT-PCR, antibody titers for previous infection for patients with ophthalmic complaints or CT of the paranasal sinuses to look for sinusitis along with a scan for the chest in high risk patients by physicians treating COVID-19 cases need to be advised conscientiously and logically. Ophthalmologists are also encouraged to report cases seen in association with COVID-19 to add to the pool of knowledge on a global level.
References


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