

Acute graft rejection in a COVID-19 patient: Co-incidence or causal association?

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A 32-year-old man with a clear and compact graft following a penetrating keratoplasty 6 years back, developed an episode of acute graft rejection, coinciding with the COVID-19 disease. Subsequent to the infection with the novel coronavirus, he developed symptoms of acute graft rejection concurrent with the development of respiratory distress and peak systemic symptoms. This was the phase of cytokine storm as evidenced by the raised inflammatory markers in his blood tests. Such a case of acute corneal graft rejection coinciding with SARS-CoV-2 infection has been reported only once in the literature and this unique association needs to be researched further.

Key words: Acute corneal graft rejection, COVID-19, cytokine storm, SARS-CoV-2

Coronavirus disease-2019 (COVID-19) has impacted the lives of millions around the world and its effect on various organs and systems of the body is being extensively studied. The ocular manifestations of the disease have also been reported, the most common of which is conjunctivitis.^[1,2] There have been reports of the disease-causing acute rejection and functional organ impairment in patients with liver, kidney and pancreatic transplantation, and how these patients who are on immunosuppression therapy are more susceptible to the disease with more severity.^[3,4] But there exists a lacunae in literature with regards to the effect of COVID-19 on corneal grafts. In our knowledge, only one case has been reported so far of acute corneal graft rejection in a COVID-19 patient.^[5]

Case Report

We report a case of a 32-year-old man who had undergone right eye (OD) penetrating keratoplasty with cataract extraction and posterior chamber intraocular lens implantation 6 years

back for an indication of traumatic leucomatous corneal scar with cataract, subsequent to ocular trauma and corneal tear repair. He had been on regular follow-up and had been diagnosed with secondary glaucoma. Till his last follow-up 2 months back, he was on multiple topical anti-glaucoma medications (combination of brimonidine 0.2% with timolol 0.5% eye drop twice/day and travoprost 0.004% eye drop once/day) and 1% prednisolone eye drop once/day. He was maintaining a best-corrected visual acuity (BCVA) of 20/60, a clear graft and an intraocular pressure within normal range in the right eye (the last documented being 14 mmHg). His left eye (OS) had an uncorrected visual acuity of 20/20 with a normal anterior and posterior segment. Around a month after his last follow-up visit, he developed symptoms of sore throat, fever and malaise for which he got tested for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The reverse transcriptase-polymerase chain reaction (RT-PCR) for the novel coronavirus was positive. He subsequently developed respiratory distress and needed monitoring and treatment in the intensive care unit. His blood tests revealed raised pro-inflammatory markers, C Reactive Protein (4.21 mg/L; reference range ≤ 3 mg/L), Lactate Dehydrogenase (242 U/L; reference range 125–220 U/L) and Interleukin 6 (23.55 pg/mL; reference range 0–7 pg/mL). During this time he noticed a sudden decrease in vision, redness and discomfort in his right eye, which occurred in spite of continuance of his anti-glaucoma medications and the maintenance dose of 1% prednisolone eye drop once daily. The patient presented to us three weeks after the acute episode. On examination OD vision was finger counting close to face with presence of multiple epithelial bullae, diffuse stromal edema, few descemet folds and keratic precipitates on the endothelium [Fig. 1]. The anterior chamber details were hazy, the intraocular pressure was 10 mm Hg but the optic disc details were not visible. The diagnosis was made of OD acute graft rejection and he was started on half-hourly 1% prednisolone eye drop. On subsequent follow-ups the graft clarity improved to some extent but epithelial and stromal edema persisted. Till his last visit, at 4 weeks from presentation, he had a BCVA of finger counting 3 m and persisting graft edema. Informed written consent was obtained from the patient regarding usage of clinical reports and pictures for research and publication purposes.

Discussion

Our case throws light on the unique possibility where acute graft rejection can occur in the setting of diseases like COVID-19 with multi-organ involvement, wherein each system has a different manifestation of the underlying inflammation.

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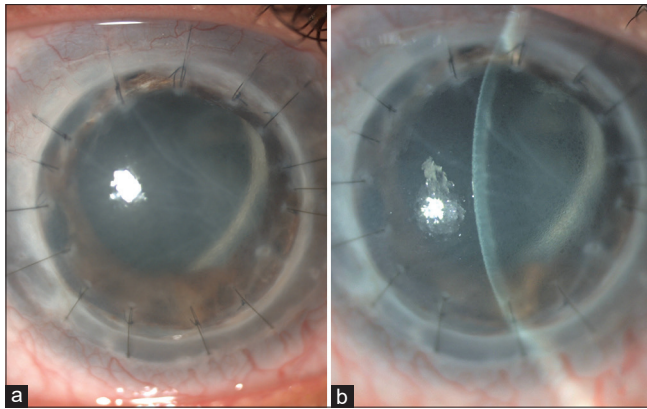


Figure 1: (a) Diffuse illumination slit lamp picture of the Right Eye (OD) showing a cloudy graft with visible descemet folds. (b) Slit beam image of OD showing extent of epithelial and stromal edema with multiple bullae

Cornea is an immunologically privileged site, which is responsible for the high rates of success of corneal transplantation surgeries in comparison to other organs.^[6] There are various factors that contribute to this unique state of the eye and maintain the delicate balance between inflammation, healing and prevention of rejection of allo-grafted corneas.^[7,8]

It is now a well-known fact that SARS-CoV-2 gains access to the human tissues via attachment to specific angiotensin-converting enzyme-2 (ACE2) receptors which are present in various organs of the body including the corneal and conjunctival epithelium.^[9] In advanced stages of the disease there is widespread tissue destruction and possible multi-organ failure which has been attributed to a kind of “cytokine storm”. It is a form of immune dysregulation characterized by the overproduction of pro-inflammatory cytokines (like IL-6, IL-1, IL-2, TNF amongst others) and the changes of differentiation and activity of T lymphocytes (particularly CD4+ T cells).^[9,10] Graft rejection is also mediated by cytokines and other pro-inflammatory mediators and adhesion molecules, which in normal circumstance are down-regulated by the protective mechanism of cornea immune privilege, but might become overwhelmed in COVID-19 disease.^[6,7]

Local factors like trauma, inflammation and surgery are known to override the normal mechanism of immune-privilege, but it is cases like these that make us ponder regarding the role of systemic immune dysregulation which occurs in viral diseases like COVID-19. The patient did not have other associated factors which might have attributed for the rejection episode, like clinical condition with high risk for rejection,^[6] noncompliance or re-graft surgery. Hence, the need to further understand what and how the acute rejection was triggered,

and realise that we are still not fully aware of the underlying complexities of this phenomena.

Conclusion

A lot has been researched on the mechanism of graft rejection and the pathophysiology of COVID-19 disease, but the possible inter-play and the causal effect relationship between the two still needs to be explored.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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