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AU1) Please spell out the abbreviations "BMI and IgG" in the text.

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Acute Corneal Endothelial Graft Rejection With Coinciding COVID-19 Infection

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Purpose: To report a case of acute corneal endothelial graft rejection with the concurrent onset of coronavirus disease 2019 (COVID-19) symptoms.

Observations: A 31-year-old African American woman with a history of asthma, sleep apnea, obesity (BMI of 40), and bilateral keratoconus was noted to have acute corneal endothelial graft rejection 3 months after uncomplicated penetrating keratoplasty of the left eye. The patient developed dysgeusia and subjective fever on the same day as ocular discomfort, and she was subsequently diagnosed with COVID-19 with only these 2 classic symptoms of the viral infection.

Conclusions: Severe acute respiratory syndrome coronavirus 2 is known to cause conjunctivitis and has demonstrated transmissibility through ocular secretions. Acute immune and inflammatory dysregulations have been seen in cases of COVID-19 through various mechanisms. COVID-19 infection may potentially compromise ocular immune privilege contributing to acute corneal graft rejection.

Key Words: COVID-19, SARS-CoV-2, coronavirus, corneal graft rejection, acute graft rejection

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Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a pandemic worldwide. The major ocular manifestation known to date is viral conjunctivitis. This is potentially due to relatively high conjunctival expression of angiotensin-converting enzyme 2 (ACE2), a functional receptor for COVID-19.[1,2] ACE2 is a part of the renin-angiotensin system, which is a powerful regulator of inflammatory responses. Immune dysregulation induced by SARS-CoV-2 has been found to play an important role in the pathophysiology of organ damage particularly affecting organs with high ACE2 expression.[2–4]

Corneal transplantation has a low graft rejection rate because of ocular immune privilege, which can be compromised by increased immune dysregulation. We report a novel case of acute corneal endothelial graft rejection after penetrating keratoplasty (PKP) in the setting of concurrent SARS-CoV-2 infection.[1]

CASE SUMMARY

A 31-year-old African American woman with a history of asthma, sleep apnea, obesity, and keratoconus underwent PKP of the left eye. Surgery was performed with an interrupted suture technique with 10-0 nylon suture, and the patient had an uncomplicated operative and early postoperative course without signs of graft rejection. Three months after surgery, she presented with new onset pain, redness, and worsened vision in the left eye for 2 days. The patient's uncorrected visual acuity in the left eye was finger counting at 1 foot with improvement to 20/250 with pinhole, which was decreased from the previous uncorrected visual acuity of 20/200 pinhole 20/80. The examination revealed 1+ conjunctival injection, a full-thickness corneal graft with 2+ microcystic and stromal edema, and diffuse keratic precipitates involving only the donor graft. No neovascularization of the host or donor cornea was noted. Otherwise, the examination was stable from the previous. The patient endorsed full compliance with the postoperative regimen of prednisolone acetate 1%, and it was confirmed with her pharmacy that the medication was refilled 3 times leading up to the date of presentation. The diagnosis of acute endothelial rejection was made, and the patient was administered topical and oral steroids.

Five days after the onset of ocular symptoms, the patient tested positive through polymerase chain reaction for SARS-CoV-2, and she also tested positive for SARS-CoV-2 IgG antibody one month later. Other than subjective fever and dysgeusia beginning the same day as her ocular symptoms, she had no other common symptoms of COVID-19 such as chills, sore throat, cough, shortness of breath, or gastrointestinal upset.

Six weeks after the onset of endothelial rejection, the patient was noted to have improvement in the keratic precipitates, but stable corneal edema. She remained free of other typical symptoms of COVID-19. Three months after the initial corneal endothelial rejection episode, SARS-CoV-2 polymerase chain reaction was repeated and resulted negative. Two days later, the patient underwent repeat PKP. At the postoperative 1-month visit, the patient's best corrected visual acuity was 20/40 and the graft remained clear without any signs of rejection.

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DISCUSSION

The cornea is the most commonly allotransplanted tissue in the United States with a low rate of graft rejection because of ocular immune privilege. Antigens may be sequestered in the eye without eliciting an immunological reaction. Proinflammatory states can also disrupt the balance of immunoregulatory responses that allow for graft survival by allowing access of otherwise absent antigen presenting cells to protected graft sites.[5,6]

To our knowledge, this is the first reported case of acute corneal endothelial graft rejection in the setting of COVID-19. The patient's postoperative course lacked signs or risk factors for graft rejection such as corneal neovascularization or medication noncompliance.

It has been established that SARS-CoV-2 acts through its functional receptor ACE2 for cellular infection. ACE2 expression in various tissues is commensurate with the clinical pathology seen in the lungs, intestines, heart, and kidneys.[2] Organs with high ACE2 expression are vulnerable because of cellular damage by 2 mechanisms, inadequate adaptive immune response in early viral replication and excessive innate immune response in late disease.[4] Although it is unclear whether COVID-19 has any causal effect in this patient's acute graft rejection, it is conceivable that a proinflammatory microenvironment induced by the virus may have compromised corneal ocular immune privilege and increased the patient's susceptibility for rejection.

REFERENCES

1. Zhang BN, Wang Q, Liu T, et al. Expression analysis of 2019-nCoV related ACE2 and TMPRSS2 in eye tissues [in Chinese]. *Zhonghua Yan Ke Za Zhi.* 2020;56:E011.
2. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature.* 2003;426:450–454.
3. Cao X. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol*. 2020;20:269–270.
4. Shi Y, Wang Y, Shao C, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ*. 2020;27:1451–1454.
5. Perez VL, Foulsham W, Peterson K, et al. (2020) pathophysiology of corneal graft rejection. In: Colby K, Dana R eds. *Foundations of Corneal Disease*. Springer; 2020:89–96. AQ:3
6. Chong EM, Dana MR. Graft failure IV. Immunologic mechanisms of corneal transplant rejection. *Int Ophthalmol.* 2007;28:209–222.