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THE SEQUELAE OF BILATERAL CONJUNCTIVITIS AS AN INITIAL PRESENTATION OF PRESUMED COVID-19-POSITIVE FEMALE

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ABSTRACT

Background and Objective

Presented is a case of a 28-year-old female, who was diagnosed with presumed COVID-19 (SARS-CoV-2) and the sequelae of her bilateral conjunctivitis. Since December 2019, the presence of severe acute respiratory syndrome COVID-19 has swept worldwide, infecting over 170 million to date and counting. It hasbeen discovered that the virus can make its way to the eyes due to an abundance of human angiotensin-converting enzyme-2 on the conjunctiva. There are limited reports accounting for bilateral keratocon-junctivitis associated with SARS-CoV-2, and even less reporting as the initial symptom and the sequelae of the ocular findings that can be associated with a COVID-19 positive patient. In this report, the signs, symptoms, management, and treatment of COVID-19 related keratoconjunctivitis will be discussed.

Methods

Presented is a case of a 28-year-old female diagnosed with presumed COVID-19 and the sequelae of her bilateral conjunctivitis.

Result

A 28-year-old female initially presented to her local emergency room on 7/9/2020 for bilateral red eyes and loss of taste and smell. She tested positive for COVID-19 at that time via a polymerase chain reaction nasopharyngeal swab. There was no conjunctival swab or serology testing of her tears performed. Her ocular symptoms persisted for an additional 3 weeks when she finally presented to our clinic, with bilateral keratoconjunctivitis, after testing negative for the virus 14 days prior.

Conclusion

This case presents findings of an initial presentation of bilateral conjunctivitis secondary to presumed COVID-19. The sequelae of the patient's ocular findings after testing negative for COVID-19 were of specific interest. This case provides a resource to help guide eye care professionals in proper questioning of those diagnosed with COVID-19 about ocular symptoms they had initially, as well as symptoms that occurred after systemic resolution of the virus infection. Furthermore, this case can help educate eye care professionals on the possible sequalae, management, and treatment of COVID-19-related keratoconjunctivitis to ensure full resolution of its effect and provide a good visual outcome for patients. We will continue to learn more about COVID-19 and its effects on the eye as well as the effect of COVID-19 vaccines on ocular manifestations of the virus.

Keywords: COVID-19, red eye, conjunctivitis, keratoconjunctivitis, cytokine storm

INTRODUCTION

The first cases of SARS-CoV-2 (COVID-19) were reported from China in December 2019.[1] Since then, more than 545 million people have been infected by the virus worldwide, resulting in over 6.4 million deaths.[2] In the United States alone, there have been over 87 million reported cases and over 1 million deaths.[2] The most common symptoms of the COVID-19 virus include fever, chills, cough, headache, difficulty breathing, muscle aches, loss of taste and smell, and sore throat. Although conjunctivitis can be a rare symptom of COVID-19, it is the most common ocular manifestation of the disease.[3,5]

The virus is thought to be transmitted person-to-person via aerosol respiratory droplets. These droplets come in contact with the nose, mouth, or eyes during close contact. These droplets containing SARS-COV-2 bind highly to angiotensin-converting enzymes type 2 (ACE2) receptors found in the nose, mouth, lungs, and ocular tissues.[6] Therefore, the infection causes damage to these tissues resulting in symptoms most commonly related to the virus. Although the COVID-19 virus can easily enter through the eyes, it does not always cause direct damage to the ocular tissues, making conjunctivitis an uncommon sign. It instead stays contained in the tears and enters the nose and throat via the nasolacrimal duct.[1] One reason may be that the eyelids, lashes, and tears help create a barrier to direct contact with the cornea and conjunctiva. Another potential reason is individuals do not touch their eyes as much as they touch their nose and mouth.[7] Additionally there is a limited amount of ACE2 receptors in the cornea and conjunctiva compared to the other tissues affected during active infection.[7]

Although conjunctivitis or keratoconjunctivitis may not be a common symptom of the COVID-19 infection, it is becoming more recognized as either a presenting symptom or an associated symptom. However, at this time, it is unknown if the virus can cause more than keratoconjunctivitis in the eyes of humans or if increased viral load has any impact on the extent of ocular manifestations.[4] Therefore, the sequelae of COVID-19 conjunctivitis and keratoconjunctivitis needs to be further understood as it presents differently case by case.

The impact of vaccination for COVID-19 will likely affect the number of cases that are presented to healthcare providers, including optometrists and ophthalmologists. At this time, there have been known ocular manifestations related to the available vaccines for SARS-CoV2,[14] but due to the number of different strains found recently, there still may be new ocular manifestations of the virus.

CASE REPORT

Initial Visit

A 28-year-old black female presented to an emergency room (ER) in South Chicago on 7/9/2020 (Figure 1A) for bilateral (OU) red eyes with associated loss of taste and smell that started the previous day and worsened progressively. She never experienced any other symptoms or fever. Per the patient, she was tested for COVID-19 via polymerase chain reaction (PCR) nasopharyngeal testing at the ER visit, which resulted in a positive test result. She quarantined as recommended for 14 days. At the first ER visit (7/9/2020), she was treated with ophthalmic trimethoprim/polymyxin B four times a day

FIG. 1. All photographs provided with the patient's permission. (A) Day one of symptoms from patient's cell phone photography; (B) Day 2 AM; One day after starting trimethoprim/polymixin B QID OU; (C) Day 2 PM; (D) Day 4 AM; One day after switching to Ofloxacin QID OU; (E) Day 4 PM; (F) Day 5; (G) Day 6; (H) Day 8; Likely when the cytokine surge resulting in increased hyperemia; (I) Day 14; (J) Day 18; Redness slightly improved, but vision worsened.

(QID) in both eyes on 7/9/2020, but her eyes began to hurt after instillation of the drops prescribed. She returned to the ER a couple of days later due to new symptoms of itching, pain, and swelling of lids with increased redness (Figures 1B and 1C). The managing physician believed that she was having an allergic reaction to trimethoprim/polymyxin B and switched her to ofloxacin eye drops 4 times a day in both eyes. Her red eyes were resolved within 2 weeks (Figure 1G).

She presented back to our clinic on 7/30/2020, 3 weeks after her initial ocular symptoms, with complaints of persistent dry eyes and blurry vision. She stated that she did not wear contact lenses in either eye nor had any recent trauma. She had discontinued ofloxacin 10 days prior and was not using any other topical medications for her eyes. Prior to this visit, she tested negative for COVID-19 (with PCR nasopharyngeal swab testing) on 7/16/2020, 7 days after her initial symptoms.

Her entering uncorrected visual acuities were 20/70 OD and 20/200 OS. Pinhole testing improved vision to 20/25 OD and 20/150 OS. Her previous manifest refraction was +1.75 −1.00 X165 OD and +7.50 −1.00 X003 OS. She had been diagnosed with refractive amblyopia OS at our clinic 1 year prior with a best correct visual acuity of 20/20 in the right eye and 20/125 in the left eye. A dry refraction was performed and found measure +1.50 −1.75 X165 in the right eye, improving distance and near visual acuity to 20/30. While the dry refraction in the left eye measured +8.50 −3.00 X003, improving distance visual acuity to 20/100.

Her slit lamp findings revealed equal diffuse grade 1 conjunctival injection OU with seven subepithelial infiltrates (SEIs) OD (Figure 2) and four SEIs OS (Figure 2) with diffuse grade 2 punctate epithelial erosions (PEE) OD only. PEE staining was observed using sodium fluorescein (NaFl). There was no palpebral conjunctival reaction in either eye. Her intraocular pressures (IOP) were 7 mmHg OD and 8 mmHg OS via Goldmann applanation tonometry with NaFl and proparacaine hydrochloride 0.5% ophthalmic solution USP, respectively (Table 1). The patient was dilated with 1% tropicamide and 2.5% phenylephrine at the examination, and her posterior pole findings were unremarkable in both eyes. A dilated refraction found +1.50 −1.75 X165 OD with stable distance acuity at 20/30 and +6.50 −3.00 X003 OS, improving distance visual acuity to 20/80. Cirrus optical coherence topography was performed to rule out any optic nerve or macular

FIG. 2. Initial visit to our clinic, (22 days after initial symptoms) in office slit lamp photos: Bilateral appearance. Subepithelial infiltrates and corneal edema. First visit to our eye clinic.

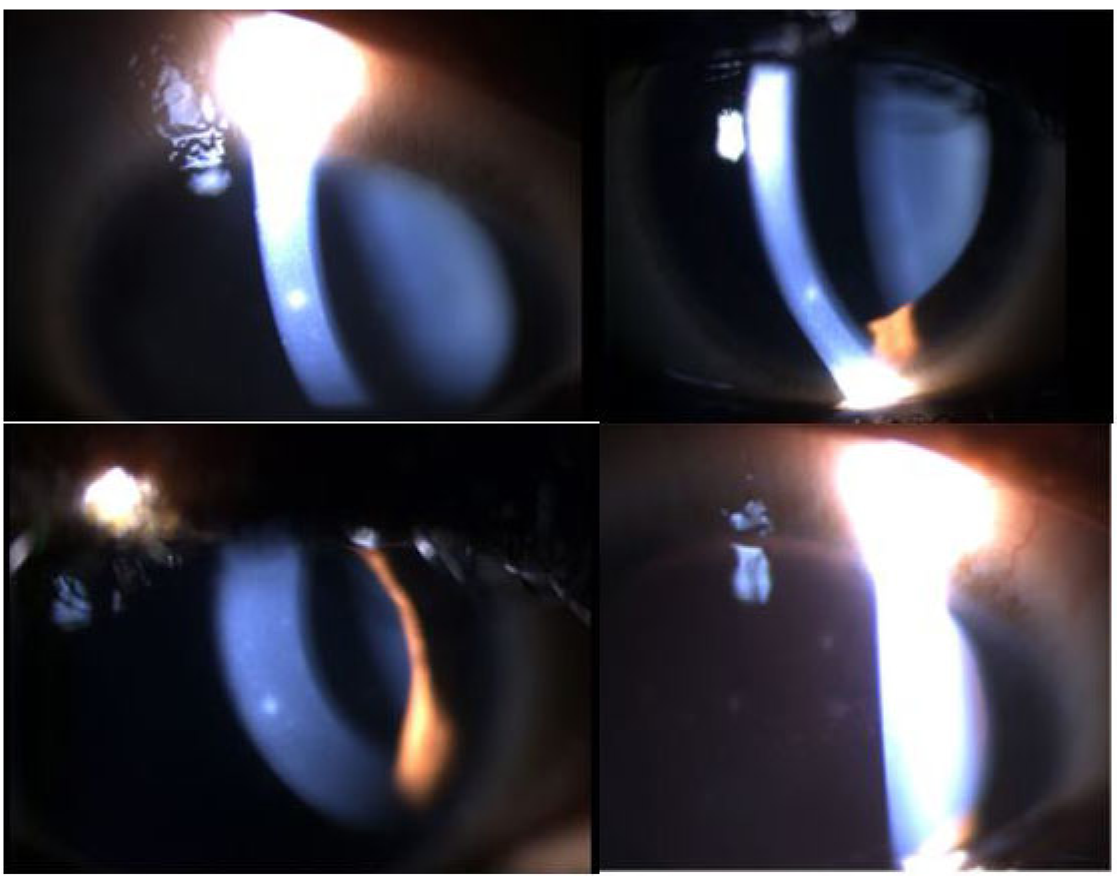


TABLE 1 Clinical findings prior to her infection with COVID-19, her initial visit, and follow up visit after being diagnosed with COVID-19.

Date	9/13/19	7/30/20	8/20/20
VAsc	OD: 20/20- OS: 20/125	OD: 20/70+1 PH 20/25 OS: 20/200+1 PH 20/150	OD: 20/30-1 PHNI OS: 20/125 PHNI
SLE	OD: WNL OD: WNL	OD: 1+injection 7 SEIs diffuse PEE (–) A/C reaction OS: 1+injection 4 SEIs (–) PEE with NaFl (–) A/C reaction	OD: W&Q, 3 SEIs diffuse PEE (–) A/C reaction OS: W&Q 2 SEIs trace diffuse PEE with NaFl (–) A/C reaction
IOP	OD: 11 mmHg OS: 11 mmHg	OD: 7 mmHg OS: 8 mmHg	OD: 12 mmHg OS: 12 mmHg

NaFl = sodium fluorescein; PEE = punctate epithelial erosions; SEI = subepithelial infiltrate.

conditions, and it demonstrated normal macular and optic nerve findings OU.

She was diagnosed with bilateral keratoconjunctivitis due to presumed COVID-19 infection and was prescribed tobramycin 0.3% (3 mg)/dexamethasone 0.1% (1 mg) drops QID in both eyes (OU) to decrease the inflammation of the cornea, while covering for any bacterial infiltration. In addition, preservative-free artificial tears (PFATs, carboxymethylcellulose sodium [1.0%]) were prescribed 8 times a day OU to improve the ocular surface. The patient was scheduled for a follow-up appointment in 2 weeks due to its mild, inflammatory appearance.

Follow Up Visit #1

The patient missed her 2nd week appointment for unknown reasons but returned on 8/20/2020 (about 3.5 weeks later), and it was noted that her symptoms had improved. Her entering uncorrected visual acuities improved to 20/30 OD which improved to 20/20 with pinhole testing, and 20/125 OS with no improvement with pinhole. The bulbar conjunctival injection had completely resolved in both eyes, and the SEIs had improved; only three remained in the right eye and two in the left eye. IOP at this visit was 12 mmHg in both eyes (Table 1). She stated that she never received the tobramycin 0.3% (3 mg)/dexamethasone 0.1% (1 mg) from the pharmacy because her insurance did not cover it, but she did use the PFATs as directed. Four days after her initial visit, she did call to confirm the situation with her insurance and the pharmacy was contacted and it was arranged to be covered and they would call the patient to pick it up. It is unknown why the patient did not start the drop, but it was confirmed that she was only using the PFATs at the time of the 8/20/2020 appointment. Because her corneal infiltrates improved in both eyes she was directed to continue with the PFATs 4 times/day OU only. The patient was directed to follow up in 1 month. The plan was to monitor her corneas until full resolution, but she did not show up for her next follow-up. The patient was contacted to reschedule her appointment, but she failed to call back or return to our eye clinic for this condition.

DISCUSSION

Ocular involvement of the infection of COVID-19 is rare.[4] Understanding the mechanism of how the virus affects and invades the body may provide further information on management of sequelae in our patient. The SARS-CoV-2 virus has an S protein with S1 and S2 subunits.[1] The S1 subunit utilizes human angiotensin-converting enzyme 2 (hACE2) to bind and infect human cells.[1] This subunit has a much higher binding affinity for hACE2 than previous SARS strains, which is why this strain has increased virulence and infection rates. The majority of hACE2 receptors are found in the respiratory tract and gastrointestinal (GI) system, which is why COVID-19 predominantly affects the lungs, and other common symptoms such as sore throat, cough, diarrhea, and nausea. There is a small number of hACE2 receptors found on the conjunctiva, which allows the virus to infect the eyes. Wilcox et al. determined that the virus travels to the eye more commonly after systemic infection due to the lack of transmembrane serine protease 2 (TMPRSS2) and furin proteins on the conjunctiva.[3] These proteins regulate protein activation of viruses in epithelial cells, found mostly in the respiratory and GI cells. Although these proteins are found in conjunctival tissue, they are rare, making it a possibility to have the conjunctiva affected after systemic infection instead of directly through the cells of the conjunctiva.[3,8] Guo et al. examined 1099 patients who tested positive for COVID-19 and found that only 0.8% had associated conjunctival congestion.[9] Wu et al. found less than 6% of the COVID-19 patients had active SARS-COV2 RNA in the conjunctival tissues.[3] It is even more rare for ocular symptoms to be one of the presenting symptoms of COVID-19. Chen et al. found that of the 534 COVID-19 patients between the ages of 40 and 50 years old, less than 5% presented with conjunctival congestion, and only three patients had it as the initial symptom.[8] He also found that the top three ocular symptoms of patients with COVID-19 were dry eye, blurred vision, and foreign body sensation.[10] Other studies found ocular symptoms of hyperemia, chemosis, epiphora, photophobia, swollen or sore eyelids, and mucus discharge. Cheema et al. and Chen et al. also found signs of conjunctival follicles, SEIs, keratitis, and pseudo-dendrites in patients with COVID-19.[5,10] Chen et al. stated that although viral loads of the disease were lower on the conjunctiva than the nasopharyngeal tissue or saliva, it can last up to 19 days on the conjunctiva.[10] Based on current literature, exposure of the ocular surface to SARS-COV-2 could lead to systemic infection due to the drainage of the virus via the nasolacrimal duct that would lead to the respiratory tract.[5] Therefore, there are two different theories regarding whether systemic COVID-19 causes ocular manifestations; eyes act as an entry point for the virus, and/or the virus causes direct compromise to the ocular tissues.

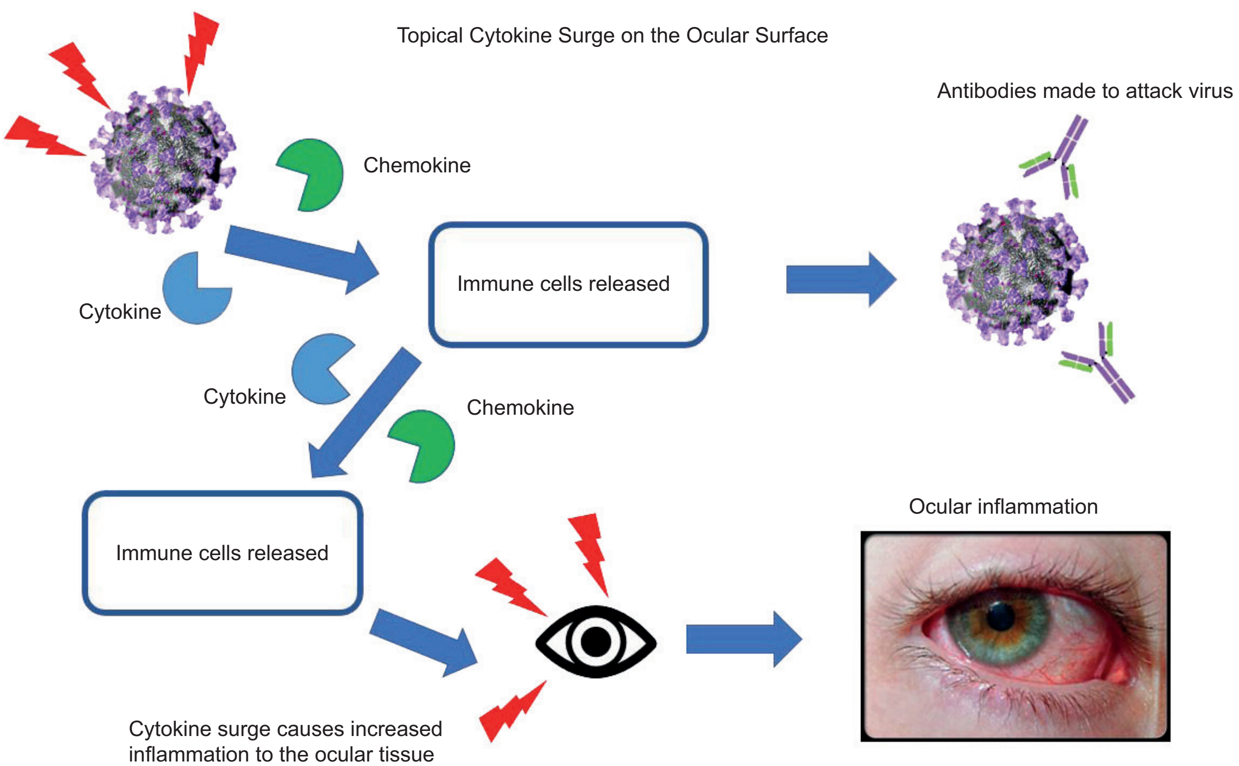
The patient presented in this case had bilateral keratoconjunctivitis as the presented initial symptom of COVID-19. Because she came to us weeks after recovering from the virus, a conjunctival swab or serology of her tears was not obtained. An adenovirus test to rule out other viral causes was also not obtained. Epidemic keratoconjunctivitis (EKC) is considered highly differential based on similar ocular manifestations to this patient; however, the course of EKC is typically 2–14 days, and once resolved it does not typically return.[11] This patient's course was much longer and appeared to worsen during the course. EKC also generally starts in one eye before becoming bilateral, whereas this patient experienced symptoms bilaterally. This case was interesting due to persistent bilateral ocular symptoms even after testing negative for COVID-19 on 7/16/2020. The patient had no history of eye rubbing, ocular seasonal allergies, cold sores, or sinus infections, which led to belief that conjunctivitis was an initial symptom of COVID-19 when she presented to the ER and part of the sequalae of COVID-19-related keratoconjunctivitis.

As in this patient, prolonged or even delayed ocular symptoms have been present among patients with COVID-19. Both Chen et al. and Guo et al. presented COVID-19 cases that had delayed ocular signs and symptoms related to COVID-19.[9,10] Guo et al. reported a case that had delayed monocular conjunctivitis, which was resolved in 6 days, only to return 5 days later as bilateral keratoconjunctivitis.[9]

The patient presented in this case had persistent ocular symptoms; however, the viral load in the eye was not measured, so it could not be confirmed whether the virus was detected on the conjunctiva or the tears, only that she tested systemically via a positive nasopharyngeal test for COVID-19 at the time her eye symptoms began. Guo et al. presented a case where SARS-CoV2 was not detected in the eye; however, the patient experienced ocular signs and symptoms.[9] He and others believed that this could be due to an autoimmune response, "topical cytokine surge," and not the virus itself invading the ocular tissues.[2] The case presented here showed similarities in persistence and changing symptoms. She demonstrated red, watery eyes as presenting symptoms when diagnosed with COVID-19 (Figure 1A), but these symptoms were resolved within 2 weeks; however, the patient began to experience foreign body sensation and blurred vision after the resolution of the presumed conjunctivitis and testing negative for the virus (Figure 1H).

The "topical cytokine surge" is thought to occur when a virus attacks a tissue of the body. Cytokines and chemokines respond against the virus and mediate various immune cells, which aid in building our immunity against a virus. However, in SARS-CoV2, the increase in specific inflammatory factors involved in the pathogenesis of COVID-19 sent to specific tissues upset the immune regulatory network via the constant self-amplification of the positive feedback loop.[12] This therefore, results in a "cytokine surge" in the ocular tissues, specifically the conjunctiva and the cornea (Figure 3). Regarding COVID-19, it is these "cytokine storms" that might be the main reason that this virus is so destructive compared to other flu-like viruses.[12]

FIG. 3. Example of cytokine surge reaction on the ocular surface. Virus invades tissue via mouth, nose, or eyes and triggers the production of cytokines and chemokines, causing a release of immune-related cells. Most often these cells help the body make antibodies to fight off the virus, but in some cases the release of these immune cells causes more cytokines and chemokines to be released.



The recommended treatment for a "cytokine surge" involves dampening the immune response; therefore, a topical steroid would be recommended in treating ocular manifestations of those diagnosed with COVID-19. In the case presented, an antibiotic–steroid combination was prescribed because of the inability to confirm the true etiology behind the keratoconjunctivitis. It was recognized by the presenting SEIs that an inflammatory process was occurring and a topical steroid would be an appropriate treatment.

The patient never received the topical antibiotic–steroid drop, and the condition was assumed to improve alone with PFATs, which is the typical treatment for viral conjunctivitis not related to herpes. Because the patient partially resolved with supportive therapy alone after her visit, it does support that the presenting keratoconjunctivitis was not bacterial or herpetic in nature. This might also explain that the epithelial infiltrates were still present after treatment with PFATs alone, and that if a steroid was used, the infiltrates might have fully resolved by the time of her follow-up visit. However, the patient did seek care for continued decrease vision and irritation after treatment with an antibiotic prescribed by the ER. Suggesting that if treated with a topical steroid at the initial visit, her symptoms could have resolved sooner and possibly have prevented a cytokine resurgence.

As demonstrated from the patient's presentation from Day 8 to Day 14 (Figure 1H), her conjunctival hyperemia, blurred vision, and keratitis appeared to worsen, indicating a possible cytokine surge in the cornea and conjunctivia. This also suggests the importance of close follow-up for patients with presumed COVID-19-related conjunctivitis or keratoconjunctivitis, especially when an ocular surface culture cannot be performed. Close monitoring will help determine whether topical medications prescribed, such as PFATs and/or an ophthalmic steroid, are effective in treating keratoconjunctivitis. It is especially important to monitor closely for a cytokine surge or other ocular manifestations of COVID-19 that could occur even after the resolution of the conjunctivitis or keratoconjunctivitis.

Several different vaccines have been administered across the world to combat the COVID-19 virus, and there are findings which show that vaccines could cause ocular manifestations, but it is still unknown if there is any direct protection to the conjunctiva from the virus after vaccination. When it comes to protecting against viral replication and shedding in the airway, a vaccine must be able to cause a "local mucosal secretory IgA response," and most COVID-19 mRNA vaccines cause only a systemic IgG response.[13] Because the conjunctiva is a mucosal tissue and likely needs mucosal immunity to prevent further spread of the virus, COVID-related conjunctivitis and keratoconjunctivitis could still possibly occur in vaccinated individuals.[13] Although, there will be a decrease in the number of COVID-19-positive patients, eyecare providers should watch for conjunctivitis as it could still occur in vaccinated individuals. It would still be important to keep COVID-19-related conjunctivitis as a differential for patients complaining of red-eye.

Conjunctivitis could possibly occur after vaccination due to inflammation brought on when receiving the COVID-19 vaccine(s). By creating an immune response, vaccines aid in building immunity, but also increase short-term inflammation in return, which is why people feel like they have flu-like symptoms, including fever, body aches, and headaches, after receiving the vaccine. The Vaccine Event Reporting System (VAERS) reported that among those who received a COVID-19 vaccine between December 2020 and December 2021, over 33% reported with conjunctivitis after receiving the vaccine.[14] Therefore, proper questioning for those with acute onset of conjunctivitis should include the date of the last vaccination or booster the patient received.

CONCLUSION

There are few reported cases of bilateral conjunctivitis associated with COVID-19 in the literature, and even less associated with corneal involvement. The research of a cytokine surge involved in COVID-19 patients can help eye care professionals better understand the sequelae of ocular manifestations that can occur with the virus and it's best use of topical steroids to prevent prolonged ocular signs and symptoms. As more is learned about COVID-19 and ocular manifestations, eyecare practitioners will be able to identify signs and symptoms of presumed COVID-related keratocon-junctivitis and establish best practices for management and treatment.

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