Case Report

Can Inactivated Coronavirus Disease 2019 Vaccine Cause Bilateral Neurotrophic Keratopathy?

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Abstract

Purpose: To present a case of bilateral neurotrophic keratopathy (NK) following an inactivated coronavirus disease 2019 (COVID-19) vaccine administration.

Methods: Case report.

Results: A 46-year-old female patient was referred to our cornea department with unhealing corneal epithelial defects in both eyes. The patient's complaints, including ocular redness, sensitivity to light and blurred vision, started 1 week after the second dose of CoronaVac® vaccine and continued to increase for 2 months. Ophthalmological examination revealed mild ocular redness, epithelial defects in the central cornea, and decreased corneal sensitivity in both eyes. No pathology that could cause NK was detected in the patient's anamnesis and tests. Treatment including bandage contact lens application, autologous serum eye drops, preservative-free artificial tears, and oral doxycycline resulted in closure of the epithelial defect on the 10th day, and on the 2-month follow-up visit, it was observed that corneal sensitivity had increased.

Conclusions: In the presented case, it is thought that bilateral NK may be associated with the vaccine due to the chronological relationship between the vaccine administration and the lack of any other explanatory etiology. A cure was achieved in a short time with appropriate treatment, and the increase in corneal sensitivity over time indicates that the corneal neuropathy was reversible. Nowadays, with the worldwide administration of COVID-19 vaccines, ophthalmologists should keep in mind that, although rare, NK manifestation may still be encountered after vaccination.

Keywords: CoronaVac, Coronavirus disease 2019, Neurotrophic keratopathy, Severe acute respiratory syndrome coronavirus 2, Side effect, Vaccination

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Introduction

The cornea is one of the most densely innervated tissues in the human body and is mainly innervated by branches originating from the ophthalmic branch (V1) of the trigeminal nerve. Although the corneal nerves are primarily sensory, they also stimulate the reflex production of tears, blinking, and the release of trophic substances that contribute to the healing of corneal wounds and the maintenance of a healthy ocular surface.[1,2] Deterioration of corneal innervation leads to neurotrophic keratopathy (NK). NK can be defined as a clinical entity in which impairment of corneal innervation leads to epithelial damage, stromal ulcers, and even perforation.[3] It is an important clinical condition requiring early intervention and close monitoring. It is estimated that NK occurs in 5 out of every 10,000 individuals.[4] NK can manifest on a wide spectrum and can be categorized into three stages. Stage 1 is characterized by the presence of cloudy corneal epithelium and superficial punctate epithelial keratopathy, without an

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epithelial defect. Recurrent or persistent epithelial defects define Stage 2. Stage 3 is characterized by corneal ulceration and melt, which may result in perforation.[5] It is known that various ocular, neurological, and systemic pathologies may be involved in the etiology of NK.

Although not frequent, Coronavirus disease 2019 (COVID-19) vaccines are known to cause various neurological complications. These neurological complications include cranial nerve involvements, such as optic neuritis, olfactory dysfunction, Bell's palsy, and paralysis of the 3rd and 6th cranial nerves.[6,7] In this study, we aimed to present a case in whom bilateral NK was detected after the second dose of an inactivated COVID-19 vaccine.

Case Report

A 46-year-old female patient was referred to our cornea department with unhealing corneal epithelial defects in both eyes. The patient's anamnesis indicated that her complaints, including ocular redness, sensitivity to light, and blurred vision, started approximately 1 week after the administration of the second dose of an inactivated COVID-19 vaccine (CoronaVac®, Sinovac Biotech, Beijing, China) and continued to increase for 2 months. The patient states that she was prescribed medications, including topical antibiotics and artificial tears, in this period, but her complaints did not resolve. The first dose of the same vaccine was administered 2 months before the second dose, but the patient did not have any systemic or ocular complaints after the first dose. Besides the ocular one, no other complaints were reported after the second dose. The patient's medical history was unremarkable, and she did not have any similar complaints before, any known systemic or ocular disease, a history of previous surgery, or COVID-19. At the initial examination, her best-corrected visual acuity (BCVA) according to the Snellen chart was 6/10 in the right eye and 5/10 in the left eye. Mild ocular redness and epithelial defects in the central cornea with slightly rolled and grayish margins were detected in both eyes by slit-lamp examination and fluorescein staining [Figure 1a-d]. No pathology was detected in the fundus examination. Since the patient did not describe pain proportional to epithelial defects, central corneal sensitivities were measured with the Cochet–Bonnet esthesiometer (Cochet–Bonnet; Luneau, France), and they were 4.0 cm in the right eye and 3.0 cm in the left eye. Bilateral NK was considered based on the current clinical findings. No abnormality was detected in the patient's routine laboratory tests, including complete blood count, blood glucose, kidney and liver function tests, and blood electrolyte levels. The patient was questioned in detail in terms of NK-related etiologies, such as ocular herpes; mechanical, chemical, or thermal ocular injury; ocular medications; contact lens use; previous corneal surgery; neurological or systemic diseases; and head trauma. However, it was thought that bilateral NK might be associated with the COVID-19 vaccine since no other possible cause was detected.

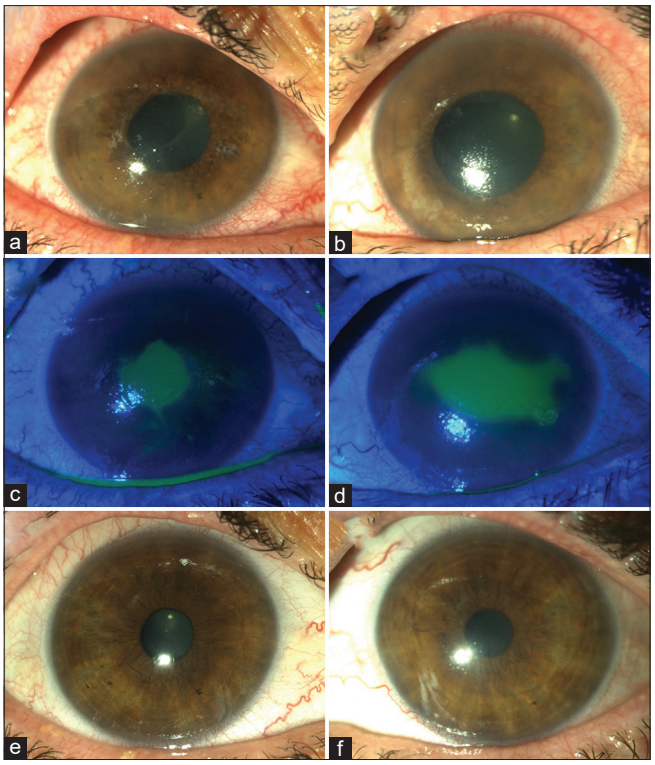

Figure 1: Slit-lamp imaging and fluorescein staining show mild ocular redness and central corneal epithelial defect with slightly rolled and grayish margins in the right eye (a and c) and left eye (b and d) at the patient's first presentation. Slit-lamp imaging at the 2-month follow-up shows closure of the epithelial defect with a slight stromal haze in the right eye (e) and the left eye (f)

A silicone hydrogel soft contact lens (Air Optix® Night and Day Aqua) bandage was applied to both eyes, and the patient was started on a treatment protocol of autologous serum eye drops q.i.d., topical antibiotics (moxiflocin hydrochloride, Vigamox®) b.i.d., preservative-free artificial teardrops containing 0.15% hyaluronic acid (Eyestil®) hourly, and 100 mg doxycycline capsule (Monodoks®) once a day orally. The patient was followed up on an outpatient basis at frequent intervals. With the recommended treatment, on the 10th day, the patient's symptoms receded. The BCVA was 7/10 in the right eye and 6/10 in the left eye; epithelial defect was closed in both eyes; and punctate epithelial erosions, stromal haze in the central cornea, and flare in the anterior chamber were observed in both eyes, although more prominently in the left eye. Preservative-free topical steroids (dexamethasone sodium phosphate 0.1%, Dexa-sine SE®) q.i.d. was added to the treatment. In the follow-ups, it was observed that the aqueous flare disappeared and the stromal haze also tended to decrease; thus, the topical steroid drops were gradually reduced.

In an examination performed 2 months after the patient's first admission, the symptoms were completely resolved. BCVA was 9/10 in the right eye and 8/10 in the left eye, and the slit-lamp examination revealed that there was no epithelial defect or punctate epithelial erosions in the cornea, no flare in the anterior chamber, and a mild stromal haze in the central

cornea [Figure 1e and f]. At this visit, repeated corneal sensitivity measurement was 6.0 cm in the right eye and 5.5 cm in the left eye.

Informed consent was obtained from the patient for the publication of the data and photographs in medical journals.

Discussion

COVID-19, which emerged at the end of 2019, caused a pandemic by affecting the entire world in a short time. Although the cause of the disease was severe acute respiratory syndrome coronavirus 2, it was observed that its effects were not limited to the respiratory system and that there was multisystem involvement, including ocular findings. The most common ocular manifestation was conjunctivitis, and in some patients, it was an initial presenting symptom. In addition, the disease can affect the ocular surface, orbit, uvea, and retina and may present with various neuro-ophthalmologic manifestations, including paralysis of the third, fourth, and sixth cranial nerves.[8] Our recently published study also showed that the patients with a history of COVID-19 had neuropathic changes in the cornea and a slight decrease in corneal sensitivity.[9]

Vaccines play an important role in our fight against the COVID-19 pandemic. Currently, there are approved vaccines against COVID-19 produced by different methods, such as whole virus, nucleic acid-based, protein subunit-based, and viral vector vaccines. We know that local or systemic side effects related to these vaccines may occur. In the current literature, it is possible to see many case reports reporting various ocular side effects of COVID-19 vaccines. In a review of these side effects, the most common ocular side effects associated with COVID-19 vaccines were listed as facial nerve palsy, cerebral venous sinus thrombosis, acute anterior uveitis, acute macular neuropathy, corneal graft rejection, anterior scleritis, panuveitis, and posterior scleritis.[10] In the same study, the authors expressed the view that since the ocular side effects caused by COVID-19 vaccines are similar to the ocular manifestations of the disease, and these side effects may result from possible common pathways between the immune response to the virus and the vaccine-mediated immune response. In a systematic review, 37 cases were included with corneal adverse events associated with COVID-19 vaccination.[11] The study identified corneal graft rejection, herpes zoster ophthalmicus, and herpes simplex keratitis as the primary complications observed in the cornea. Additional uncommon side effects were identified in a single case of conjunctival limbal graft rejection, keratolysis in one case, and peripheral ulcerative keratitis in one case. In the case outlined as keratolysis in this review, bilateral immune-mediated corneal melting and necrosis were reported in a male patient aged 48 years, 3 weeks following the administration of the recombinant viral vector vaccine (ChAdOX 1 nCoV-19).[12] The authors concluded that the presence of lymphocytes, macrophages, and eosinophils in the host cornea indicate vaccine-induced immunogenic and hypersensitivity reactions. Most of the ocular side effects reported in the literature regarding COVID-19 vaccines are related to mRNA vaccines and viral vector vaccines, and publications about inactivated vaccines are rare. In a study, in which possible inactivated vaccine (Sinopharm®)-related ocular side effects were compiled, episcleritis was reported in one patient, anterior scleritis in two patients, acute macular neuroretinopathy in two patients, paracentral acute middle maculopathy in one patient, and subretinal fluid in one patient.[13] Ocular side effects reported to be possibly related to the inactivated CoronaVac® vaccine, which was also administered in the case we presented, were endothelial corneal allograft rejection in one patient and bilateral optic neuritis in one patient.[14,15] To the best of our knowledge, there is no reported NK case associated with the COVID-19 vaccine.

Many different pathologies affecting the trigeminal nerve trace, which provides the sensory innervation of the cornea, can cause hypoesthesia/anesthesia in the cornea and ultimately NK. The most common factor in the etiology of NK is herpes viral infections, along with chemical and thermal ocular injuries, topical medications, contact lens misuse, corneal and intracranial surgeries, diabetes, and demyelinating diseases, such as multiple sclerosis.[3,5] In the case, we presented, we thought that NK might be related to the vaccine, since there was no pathology that could cause NK, and the patient's symptoms were also temporally related to the vaccine. However, since the underlying mechanism cannot be explained by a single phenomenon, it is not possible to identify a definite causal relationship. For cranial nerve palsies reported in the literature following COVID-19 vaccination, no exact pathogenesis can be identified.[6] Hypotheses suggest that nerve demyelination or localized nerve blood flow reduction is due to aberrant immune responses and immune-mediated damage.[7] The leading hypothesis for the explanation of vaccine-induced abnormal immune responses is molecular mimicry. Molecular mimicry describes the similarity between pathogenic components that are present in the vaccine and certain proteins that are present in the human body. Consequently, this similarity can lead to immune cross-reactivity, where the immune response to pathogenic components damages comparable human proteins.[16]

Treatment in NK is planned stepwise according to the severity of the disease.[5] In the case we presented, we observed that the epithelial defect was closed with bandage contact lens application, autologous serum eye drops, preservative-free artificial tears, and systemic doxycycline treatment. In addition, the increased corneal sensitivity in the patient's follow-ups suggested that the neuropathy in the cornea also improved over time.

In conclusion, although the underlying mechanism is not fully known, it is thought that bilateral NK may be associated with the vaccine due to the chronological relationship between the vaccine and the lack of any other explanatory etiology. A cure was achieved with appropriate treatment, and the increased corneal sensitivity over time indicated that the corneal

neuropathy was reversible. Nowadays, with the worldwide administration of COVID-19 vaccines, ophthalmologists should keep in mind that, although rare, NK manifestation may still be encountered after vaccination.

Declaration of patient consent

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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