

Case Report

Presumably Corneal Graft Rejection after COVID-19 Vaccination

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Keywords

Corneal graft · Graft rejection · COVID-19 · Vaccination

Abstract

We report two cases of corneal graft rejection following immunization with COVID-19-inactivated vaccine Sinopharm and describe the practical implications of this phenomenon in the clinical setting. A 36-year-old woman with a history of unilateral repeated PKP received the first dose of inactivated Sinopharm vaccine. Seven days later, she presented with symptoms and signs of unilateral corneal graft rejection on slit-lamp examination. A 54-year-old woman with a history of unilateral PKP secondary to herpes simplex keratitis (HSK) developed signs of unilateral corneal graft rejection just a week after injection of the first dose of the similar vaccine. Rejection in both patients was treated successfully with topical steroids. To the best of our knowledge, this is the first report of corneal graft rejection following the COVID-19-inactivated Sinopharm vaccine which occurred through the short period after the injection. We hypothesized that the rejection is the result of an allogenic reaction and the immunogenic role of aluminum hydroxide as an adjuvant of this type of vaccine. However, as the second case had a history of rejection following the HSK, a reactivation could not be definitely ruled out. Ophthalmologists should consider these types of adverse reactions after COVID-19 immunization and also monitor a close follow-up of graft health postimmunization. Patients should be informed about the signs and symptoms of rejection, urgent referral, and treatment.

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Introduction

Corneal immune privilege is induced both by the lack of blood and lymph vessels in the host tissue and the absence of major histocompatibility complex (MHC) class II antigen-presenting cells (APCs) in the donor tissue. Meanwhile, immunization may induce the presence of this type of cells in all the layers of the cornea and subsequently will increase the chance of rejection in the future [1]. Vaccine-induced corneal graft rejection is a rare phenomenon reported previously with influenza, hepatitis B, yellow fever, and herpes zoster vaccinations [2–5].

There have been few reports of rejection after the corona virus disease-2019 (COVID-19) immunization and with the COVID-19 vaccination rise against SARS-CoV-2 worldwide; we are expecting an increase in the number of rejections. So far research has shown that COVID-19 vaccines are congruent with the increase in specific neutralizing antibodies and CD4+ Th1 cells' responses against the virus, which are the main responsible cells in the corneal graft rejections [6]. Here, we present 2 patients with corneal endothelial graft rejection after the inactivated Sinopharm COVID-19 vaccination.

Case Presentation

Patient #1

A 36-year-old female presented with a 2-day history of painful red-eye and rapid vision loss in her left eye. She had received the first dose of the inactivated Sinopharm BIBP COVID-19 vaccine just 7 days before the appearance of her symptoms. Her past ocular history included penetrating keratoplasty (PKP) in the left eye approximately 4 years ago for corneal opacity secondary to herpes simplex keratitis (HSK). She had undergone repeated PKP in the left eye due to the failed graft approximately 1 year ago. She was receiving prophylactic oral acyclovir (400 mg bid) after the re-raft, topical steroid (fluorometholone every other night), and topical tacrolimus 0.05% (bid). On examination, the best-corrected visual acuity was 20/400 in the left eye using the Snellen chart. Slit-lamp examination (SLE) revealed endothelial and stromal corneal graft rejection in the left eye with the evidence of conjunctival hyperemia, inferior corneal edema, keratic precipitates, and diffuse subepithelial infiltration (Fig. 1a). The right cornea was healthy.

The patient was treated with topical betamethasone every 1 h for 1 day followed by every 2 h up to 7 days with gradual tapering and oral acyclovir 400 mg 5 times a day to cover any possible underlying HSK. Significant improvement was observed 14 days after the treatment, and the signs of inflammation were partially resolved (Fig. 1b).

Patient #2

The second patient was a 54-year-old female who presented with a complaint of ocular discomfort in the left eye 7 days after the first dose of the inactivated Sinopharm BIBP COVID-19 vaccine. She had a history of PKP 2 years prior due to corneal opacity secondary to HSK. The patient was receiving prophylactic acyclovir (400 mg bid) and topical tacrolimus (0.05% bid) after the re-raft. The best-corrected visual acuity of the left eye was 20/200. The subepithelial opacity and less than 5 keratic precipitates were observed on SLE. A mild flare in the anterior chamber was present (Fig. 2). Other examinations revealed no pathologic findings. The patient was treated with a topical steroid (betamethasone drops) every 1 h for 1 day reduced to every 2 h for 1 week, tapered off within 1 month. The infiltrations and KPs were resolved 2 weeks after the start of treatment. Oral acyclovir 400 mg every 5 h was also started to treat the possible recurrence of HSV keratitis.

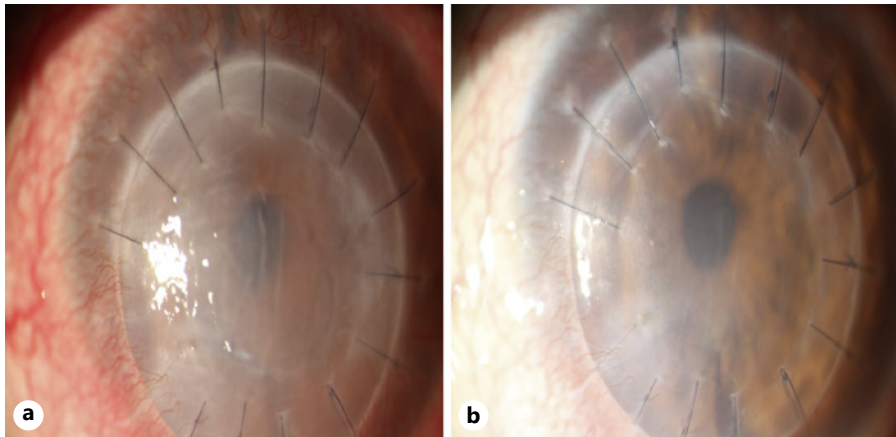


Fig. 1. Photoslit images of the patient demonstrate (a), conjunctival hyperemia, corneal edema, folds on the descemet membrane most possibly due to corneal graft rejection. Part (b) shows significant but partial resolution of the graft rejection episode.

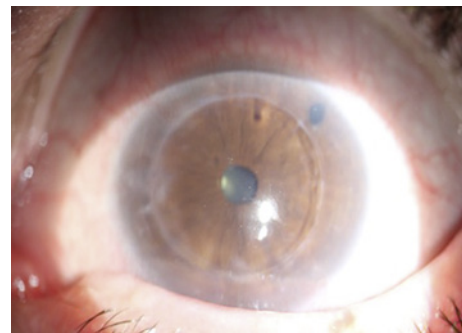


Fig. 2. Subepithelial opacities in the periphery and a few keratic precipitates in the center of the cornea are evident in the photoslit image of a patient 7 days after the first dose of COVID-19 vaccination.

Discussion

To our knowledge, the number of corneal graft rejections after COVID-19 vaccination is rising [7–17]. Interestingly, we have observed an increasing pattern in corneal graft rejection during the mass vaccination against SARS-CoV-2 in Labbafinejad Medical Center as a referral center in Tehran, Iran.

Eleven cases with acute graft rejection have been reported in the literature. The common features of these patients (summarized in Table 1) include being a regraft in the majority of patients as a risk factor, a short-time interval between two events (mean of 1–2 weeks), and PKP as the most commonly reported transplant type. The most frequent COVID-19 vaccine type reported through literature was mRNA-based and vector-based vaccines BNT162b2 [18] and AZD1222 [19], respectively. However, our report represents two cases of corneal graft rejection following PKP, occurring just a week after the Sinopharm-inactivated COVID-19 vaccine which is the first report after the inactivated-COVID-19 vaccine type so far. The inactivated Sinopharm vaccine developed by Sinopharm (Wuhan, China) is mixed with aluminum hydroxide as an adjuvant, an immunogenic substance and is supposed to be the principal reason for adverse reactions resulting from the vaccine [20, 21].

Rejection of corneal transplant following immunization has previously been reported with other vaccines including influenza [5, 22, 23] and yellow fever [2] which were in association with induction of MHC II APC by immunization. In low risk grafts, the corneal immune

Table 1. Summary of reported case reports of corneal graft rejection after COVID-19 vaccination

Study	Age	Sex	Type of graft	Vaccine type	Interval postvaccination (D for days and W for weeks)	Interval postgraft (M for months and Y for years)	Laterality	Risk factor	Treatment	Outcome
Abousy et al. [1]	73	F	DSAEK	mRNA-based	2 W after the second dose	8 Y	Bilateral	None	Topical steroid	Resolved
Simão and Kwitko [28]	63	F	PKP (x 3) LASIK	Inactivated vaccine (Sinovac)	1 D after the first dose and the second dose	4 Y (last PKP)	Unilateral	Regraft	Topical steroid and polydimethylsiloxane	Not resolved
Nioi et al. [30]	44	F	PKP	mRNA-based	13 D after the first dose	25 Y	Unilateral	None	Topical steroids + vitamin D supplement	Resolved
Rallis et al. [7]	68	F	PKP	mRNA-based	4 D after the first dose	4 M	Unilateral	Regraft	Topical steroids	Resolved
Ravichandran and Natarajan [8]	62	M	PKP	Recombinant vector-based	3 W after the first dose	2 Y	Unilateral	None	Topical steroids	Resolved
Phylactou et al. [9] Patient #1	66	F	DMEK	mRNA-based	1 W after the first dose	3 W	Unilateral	Recency	Topical steroids	Resolved
Phylactou et al. [9] Patient #2	83	F	DSAEK	mRNA-based	3 W after the second dose	3 Y	Bilateral	Regraft	Topical steroids	Resolved
Wasser et al. [10] Patient #1	73	M	PKP	mRNA-based	2 W after the first dose	1 Y	Unilateral	Regraft	Topical+ systemic steroids	Resolved
Wasser et al. [10] Patient #2	56	M	PKP	mRNA-based	2 W after the first dose	10 M	Unilateral	Regraft	Topical steroids	Resolved
Crnej et al. [11]	71	M	DMEK	mRNA-based	1 W after the first dose	5 M	Unilateral	None	Topical steroids	Resolved
Balidis et al. [12] Patient #1	77	F	DMEK	mRNA-based	1 W after the first dose	12 M	Unilateral	Regraft	Topical + systemic steroids	Resolved
Balidis et al. [12] Patient #2	64	F	PKP	mRNA-based	1 W after the second dose	3 Y	Unilateral	Regraft	Topical + intracameral steroids	Resolved
Balidis et al. [12] Patient #3	69	M	PKP	adenoviral vector-based	5 D after the first dose	22 M	Unilateral	None	Topical + systemic steroids	Resolved
Balidis et al. [12] Patient #4	63	M	DSAEK	adenoviral vector-based	10 D after the first dose	9 M	Unilateral	Regraft	Topical steroids	Resolved

Table 1 (continued)

Study	Age	Sex	Type of graft	Vaccine type	Interval postvaccination (D for days and W for weeks)	Interval postgraft (M for months and Y for years)	Laterality	Risk factor	Treatment	Outcome
de la Presa et al. [13]	27	F	LR-CLAL (x 2)	mRNA-based	2 W after the first dose	4 Y 7 M	Unilateral	Regraft	Topical steroid and systemic steroid	Resolved
Parmar et al. [14]	35	M	PKP	adenoviral vector-based	2 D after the first dose	6 M	Unilateral	Regraft	Topical and systemic steroid	Resolved
Rajagopal and Priyanka [15]	79	M	DSAEK & PKP (x 2)	vector-based	6 W after the second dose	5 Y	Unilateral	Regraft	Topical and systemic steroid	Resolved
Shah et al. [16] Patient#1	74	M	DMEK	mRNA-based	1 W after the first dose	5 M	Unilateral	None	Topical steroid	Resolving
Shah, et al. [16] Patient#2 [16]	61	F	Tectonic then optical PKP and repair	mRNA-based	3 W after the first dose	1 Y (last surgery)	Unilateral	Regraft	Topical steroid	Resolving
Shah et al. [16] Patient#3	69	F	DSAEK	mRNA-based	2 W after the second dose	6 Y	Unilateral	DM Salzmann-nodular degeneration	Topical steroid	Resolved
Shah et al. [16] Patient#4	77	M	PKP	mRNA-based	1 W after the second dose	22 Y	Unilateral	None	Topical steroid	Resolved
Yu et al. [17]	51	M	PKP	SARS-CoV-2 mRNA-1273 Moderna vaccine	3 D after the first dose	3 W	Unilateral	Regraft	Topical steroid	Not resolved

PKP, penetrating keratoplasty; DSAEK, descemet stripping automated endothelial keratoplasty; DMEK, descemet membrane endothelial keratoplasty; LASIK, laser-assisted in situ keratomileusis. DM, diabetes mellitus.

privilege could prevent the rejection episodes. This phenomenon explains the low rate of rejection after COVID-19 vaccination. Moreover, previous research has shown that corneal re-implantation can increase the risk of rejection, especially after the history of 2 or more past rejections [24]. The disruption in the mechanisms of anterior chamber-associated immune deviation and alterations in the function of APCs are responsible for higher episodes of graft rejection in patients undergoing the second keratoplasty [25]. When the disruption in immune privilege occurs, the rejection episode could be observed as early as 1 week like in our patient. The breakdown could be attributed to the presence of corneal vascularization or MHC II acting as APCs for the immune recognition of corneal donor [25].

To date, different types of COVID-19 vaccines have been used worldwide with 3 main mechanisms of action: 1. protein-based vaccines like the inactivated China's COVID-19 vaccines Sinovac and Sinopharm make up the viral protein in vitro; 2. gene-based vaccines like DNA or mRNA-based vaccines such as BNT162b2, Pfizer-BioNTech, and mRNA-1273, Moderna deliver the gene encoding a viral protein; or 3 combination of both [26, 27]. Simao and colleagues reported the rejection episode after an inactivated vaccine (Sinovac Biotech, Beijing, China) [28]. The patient had signs of endothelial graft rejection and fluid accumulation in the interface 24 h after vaccination. To the best of our knowledge, this is the first report of corneal graft rejection following the COVID-19-inactivated Sinopharm vaccine which occurred through the short period after the injection.

It is well known that the mRNA-based vaccines strongly trigger both humoral and cellular immunity which leads to an increase in SARS-CoV-2-neutralizing antibodies, antigen-specific Th1-CD4+ responses, and an increase in proinflammatory cytokines such as interferon-gamma which play a key role in allograft rejection [6]. However, the pathogenesis of graft rejection following inactivated vaccines such as Sinopharm is not yet known.

Although the causality between COVID-19 immunization and corneal graft rejection cannot be concluded from this study, the temporal association between these two events reported in our cases and through the literature might confirm the hypothesis that the immune system upregulation induced by vaccination might be responsible for this phenomenon. Moreover, Nioi et al. [29, 30] reported a similar case and used the causality assessment of an adverse event following immunization guidelines to perfectly demonstrate this relationship.

There have been few reports about the adverse effects of COVID-19 vaccination on ocular HSV and VZV reactivation such as herpes zoster ophthalmicus [31, 32], granulomatous uveitis [30], keratouveitis glaucoma [33], and herpetic keratitis. Richardson-May et al. [34] reported the first case of HSK reactivation following the COVID-19 vaccination (AstraZeneca vaccine) in an 82-year-old male with a history of previous HSK. SLE revealed reduced corneal sensation and typical dendritic lesions. Furthermore, Alkwikbi et al. [33] reported 4 cases of HSK reactivation after COVID-19 vaccination (AstraZeneca and Pfizer-BioNTech vaccine) each with typical HSK dendritic epithelial ulcers, and Song et al. [35] reported a relapsed case of disciform stromal herpetic keratitis after the Pfizer-BioNTech vaccine with typical round stromal infiltration.

However, HSK reactivation postvaccination in patients with a history of corneal grafts has been rarely reported in the literature. Li et al. [36] reported two cases of HSK reactivation following COVID-19 vaccination (Sinopharm vaccine) with a history of PKP in one of the patients. On SLE, there was a typical HSV dendritic lesion in the center of the graft. The diagnosis of recurrent herpes simplex epithelial keratitis was confirmed with PCR of lesion scrapings [36].

Both of our patients underwent PKP due to HSK. The recurrence of HSK is among the differential diagnoses with a strong possibility. However, the presence of edema in the recipient bed in the first patient is in favor of corneal graft rejection. Moreover, the lack of corneal edema in the second patient reduces the possibility of HSV infection. Due to the difficulty in exact diagnoses, both rejection and recurrence of HSV keratitis were simultaneously treated.

Although there are an increasing number of case reports supporting this hypothesis, future studies especially with high-level evidence are needed to completely demonstrate this relationship. We acknowledge that clinical observations are prone to various biases, but we believe that ophthalmologists and general practitioners should be aware of this potential risk associated with the vaccination, and patients should be counseled on the early symptom and signs of rejection.

We also recommend COVID-19 vaccine administration ahead of time for nonurgent keratoplasties and using topical betamethasone every 6 h at least 3 days before immunization. In patients with a history of HSK as the indication of keratoplasty, prophylaxis with systemic acyclovir is also recommended just before receiving COVID-19 vaccination for a 2-week duration.

Statement of Ethics

Written informed consent was obtained from the patients for publication of the details of their medical case and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Kiana Hassanpour, senior author, did the data gathering and edited the final version. Maryam Mohammadzadeh and Mina Jafari performed the literature review and helped in drafting the manuscript. Sadid Hooshmandi took the photos and helped in writing the draft. All authors read and approved the final version to submit.

Data Availability Statement

All data generated and analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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