Characteristics of endothelial corneal transplant rejection following immunisation with SARS-CoV-2 messenger RNA vaccine

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ABSTRACT

Aim We report two cases of endothelial corneal allograft rejection following immunisation with SARS-CoV-2 messenger RNA (mRNA) vaccine BNT162b2 and describe the implications for management of transplant recipients postvaccination for COVID-19.

Methods A 66-year-old woman with Fuchs endothelial corneal dystrophy (FECD) and a unilateral Descemet's membrane endothelial keratoplasty (DMEK) transplant received COVID-19 mRNA vaccine BNT162b2 14 days post-transplant. Seven days later, she presented with symptoms and signs of endothelial graft rejection. An 83-year-old woman with bilateral DMEK transplants for FECD 3 and 6 years earlier developed simultaneous acute endothelial rejection in both eyes, 3 weeks post second dose of COVID-19 mRNA vaccine BNT162b2. Rejection in both cases was treated successfully with topical corticosteroids.

Conclusions We believe this is the first report of temporal association between corneal transplant rejection following immunisation against COVID-19 and the first report of DMEK rejection following any immunisation. We hypothesise that the allogeneic response may have been initiated by the host antibody response following vaccination. Clinicians and patients should be aware of the potential of corneal graft rejection associated with vaccine administration and may wish to consider vaccination in advance of planned non-urgent keratoplasties. Patients should be counselled on the symptoms and signs that require urgent review to allow early treatment of any confirmed rejection episode.

INTRODUCTION

Although the cornea is an immune-privileged site, the most frequent cause of graft failure is allogeneic rejection.[1] Of the different types of corneal transplant procedure, rejection is reported least frequently following Descemet's membrane endothelial keratoplasty (DMEK), in which the transplanted donor tissue consists only of Descemet's membrane and endothelium.[2–4] Price *et al*[2] reported that the cumulative 5-year rejection episode rate was 2.6% in 705 DMEK procedures for Fuchs endothelial corneal dystrophy (FECD). Irrespective of whether the transplanted donor cornea is full or partial thickness, each rejection episode, even if reversed by treatment, causes irreversible loss of donor endothelial cells, which maintain corneal transparency. Progressive loss of endothelial cells results in decompensation and persistent stromal oedema with reduction in visual acuity.

The COVID-19 pandemic has seen the rapid introduction of immunisation directed against SARS-CoV-2 in an effort to limit the spread of the disease and reduce its associated morbidity and mortality.[5] With the systematic state-sponsored vaccination efforts adopted by countries worldwide, very large numbers of patients with corneal transplants have had, or are set to have, SARS-CoV-2 vaccines. We describe two cases of DMEK allograft rejection following COVID-19 immunisation and propose the possibility of a causal association.

CASE 1

Following uneventful combined right phacoemulsification, lens implantation and DMEK for FECD in a 66-year-old Caucasian woman, all findings were satisfactory at postsurgery examinations on days 2 and 7. These included full graft attachment, restoration of corneal transparency, central corneal thickness (CCT) of 525 µm and best corrected visual acuity (BCVA) of 6/6. Scheduled treatment was continued with topical dexamethasone 0.1% 2 hourly for the first 2 weeks following surgery, then reduced to four times daily. The patient received the first dose of SARS-CoV-2 mRNA vaccine BNT162b2 (Pfizer-BioNTech) on day 14 post-transplant. She presented with acute onset of blurred vision, redness and photophobia in the right eye 7 days postvaccination, on day 21 post-transplant. Full compliance with topical medication was confirmed. The patient's medical history was notable for well-controlled HIV infection (undetectable viral load, CD4+ >600 cells/mm^3) on antiretroviral therapy with Triumeq (abacavir/dolutegravir/lamivudine).

At presentation, BCVA was 6/36 in the right eye and intraocular pressure was 10 mm Hg. On slit lamp examination, anterior segment findings included moderate conjunctival injection, diffuse corneal oedema, fine keratic precipitates restricted to the donor endothelium inferiorly, anterior chamber (AC) inflammation (cells +1, no flare) and a well-positioned posterior chamber intraocular lens implant (figure 1A). The left eye was uninflamed with minimal corneal oedema secondary to FECD and early cataract. Dilated funduscopy was normal in both eyes. Anterior segment optical coherence tomography (MS-39, CSO, Florence, Italy) confirmed full graft attachment and CCT of 652 µm, which was significantly increased compared with 525 µm on earlier post-transplant review on day 7 (figure 1C,D). An AC sample was examined

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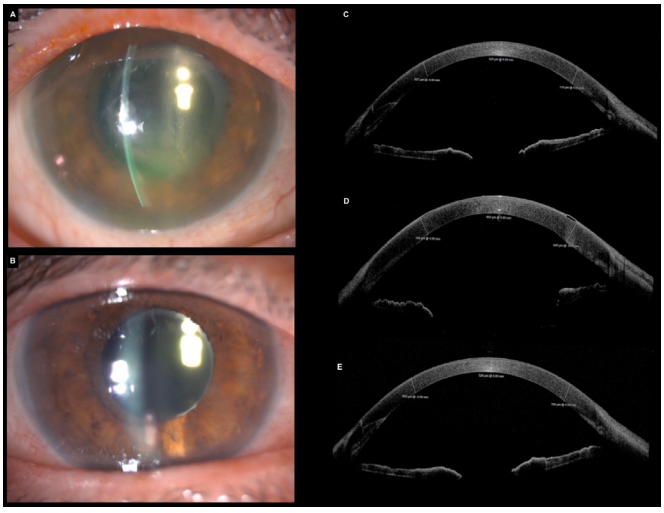

Figure 1 Early acute endothelial rejection post-DMEK following vaccination. Slit lamp image at presentation on day 7 postvaccination with rejection and corneal oedema (A), and on day 14 postvaccination and intensive treatment with topical dexamethasone showing improved stromal transparency (B). Anterior segment OCT on day 7 post-DMEK indicating full graft attachment and CCT of 525 µm (C), on day 21 post-DMEK (day 7 postvaccination) at presentation with rejection and CCT of 652 µm corresponding to observed stromal oedema and inflammation (D), and on day 28 post-DMEK (day 14 postvaccination) following increased frequency of topical steroids and CCT of 526 µm (E). CCT, central corneal thickness; DMEK, Descemet's membrane endothelial keratoplasty; OCT, optical coherence tomography.

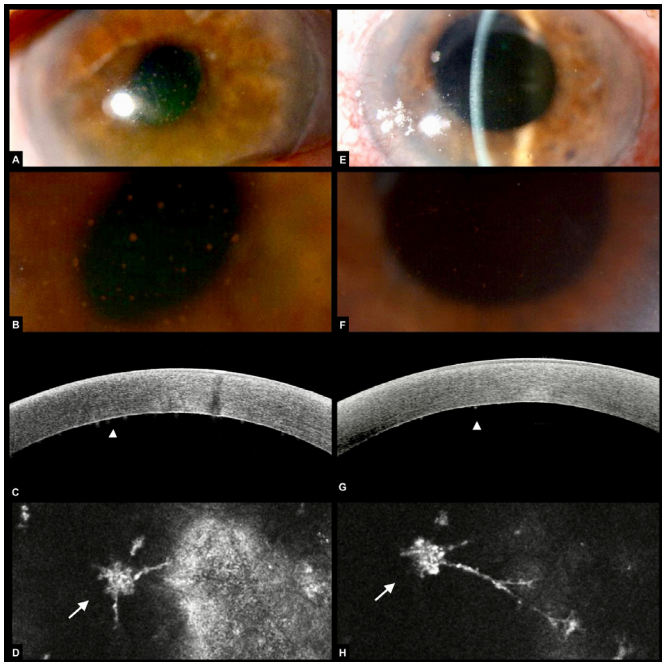

Figure 2 Bilateral simultaneous acute endothelial rejection post-DMEK following vaccination. Right cornea keratic precipitates on slit lamp (A,B) and OCT (C, marked by arrowhead) images; attached bright cells with extending processes attached to donor corneal endothelial cells (arrow) on in vivo confocal microscopy (D). Corresponding images of the left cornea (E–H). DMEK, Descemet's membrane endothelial keratoplasty; OCT, optical coherence tomography.

for any possible associated virus-induced corneal inflammation: PCR with primers for cytomegalovirus, herpes simplex virus and varicella zoster virus was negative. As clinical appearances were typical of acute endothelial graft rejection, the frequency of topical steroid was increased from four times daily to every hour.

At follow-up 3 days later, symptoms and signs of inflammation were resolving. The transplant function continued to improve on high-frequency dexamethasone drops, with clear cornea and BCVA of 6/6 7 days after presentation (figure 1B,E). The frequency of topical dexamethasone was reduced to 2 hourly for 7 days and thereafter continued four times daily according to our standard endothelial keratoplasty protocol. At the latest examination 4 weeks postrejection onset, visual acuity was good and there was no active inflammation.

CASE 2

An 83-year-old Caucasian woman presented with sudden onset of bilateral blurred vision, pain, photophobia and redness. She underwent DMEK and cataract surgery for FECD in the right eye 6 years earlier and the same procedure in the left eye 3 years earlier with replacement of an earlier Descemet's stripping enothelial keratoplasty graft. At the last examination 5 months prior to urgent presentation, BCVA was 6/6 in both eyes with bilateral functioning grafts. Topical steroid medication was discontinued at that time. The patient received both doses of the SARS-CoV-2 mRNA vaccine BNT162b2 (Pfizer-BioNTech) at 2 months (first dose) and 3 weeks (second dose) prior to the onset of symptoms.

At presentation, BCVA was 6/24 in the right eye (OD) and 6/12 in the left eye (OS). Findings on slit lamp examination included bilateral circumcorneal injection, keratic precipitates, AC inflammation and normal intraocular pressure (figure 2). Anterior segment inflammation signs were more prominent in her right eye, consistent with symptoms. Dilated funduscopy was normal in both eyes. CCT was 660 µm OD and 622 µm OS. A diagnosis of bilateral simultaneous acute endothelial graft rejection was made and treatment with hourly steroid drops was commenced. At follow-up 7 days later, signs of inflammation were reduced, both grafts were functioning well, and BCVA had improved to 6/6 in both eyes. The frequency of topical dexamethasone was reduced.

DISCUSSION

Despite the immune privilege of the cornea, immune-mediated corneal allograft rejection does occur, especially after penetrating keratoplasty in high rejection risk eyes. The effector response in endothelial rejection is characterised by AC infiltration of monocyte-derived macrophages, CD4+ and CD8+ T cells.[6] Corneal graft rejection following vaccination has been previously described in patients with penetrating or anterior lamellar transplantation[7–10] (table 1).

While there is no proof of causation, factors suggestive of a possible causal relationship include the temporal association following vaccination, and in particular the occurrence of simultaneous bilateral rejection which is rarely seen in clinical practice.

In case 1, the clear signs of an immune response directed at the donor endothelial keratoplasty graft within 21 days of transplantation suggest allorecognition by the direct pathway as one possible mechanism. Allorecognition is the earliest event in corneal transplant rejection and known in most cases to be indirect, initiated by trafficking of recipient antigen-presenting cells into the cornea and/or AC.[11] However it would be highly unlikely that any donor origin antigen-presenting cells, a prerequisite for direct allorecognition, would be transplanted as passenger cells

Table 1 Summary of reported cases of corneal graft rejection following vaccination

Study	Patient, age, laterality	Eye/episode	Vaccine	Interval postgraft	Type of graft	Interval postvaccination	Outcome
Solomon and Frucht-Pery[8]	Patient 1, 80, bilateral, simultaneous	OD/first	Influenza (trivalent vaccine for the inactivated strains of A-Beijing-32/92-H3N2, A-Texas-36/91-H1N1 and B-Panama-45/90 of the influenza virus)	11 years	PK	6 weeks	Resolved with topical and sub-Tenon's steroids and systemic steroids (80 mg prednisolone orally per day).
		OS/first	Influenza (trivalent vaccine for the inactivated strains of A-Beijing-32/92-H3N2, A-Texas-36/91-H1N1 and B-Panama-45/90 of the influenza virus)	8 years	PK	6 weeks and 3 days	Resolved with topical and sub-Tenon's steroids and systemic steroids (80 mg prednisolone orally per day).
Wertheim *et al*[7]	Patient 2, 67, unilateral	OS/first	Influenza (Sanofi-Pasteur MSD, UK)	8 months	PK	2 weeks	Resolved with topical steroids.
	Patient 3, 67, unilateral, consecutive	OD/first	Influenza (Sanofi-Pasteur MSD, UK)	7 months	PK	3 weeks	Resolved with topical steroids.
		OD/second (1 year after, following annual vaccination)	Influenza	1 year and 7 months	PK	4 weeks	Resolved with topical steroids.
Hamilton *et al*[10]	Patient 4, 33, unilateral	OD/first	Influenza (Fluvax, CSL, Parkville, Victoria, Australia)	2 years and 7 months	DALK	3 weeks	Resolved with topical steroids but residual central stromal haze with visual loss from prior to rejection.
Vignapiano *et al*[9]	Patient 5, 48, unilateral	N/A	Yellow fever	N/A	N/A	3 weeks	Resolved with topical and systemic steroids.

DALK, deep anterior lamellar keratoplasty; N/A, not available; OD, right eye; OS, left eye; PK, penetrating keratoplasty.

in a DMEK graft. An alternative possible mechanism is suggested by some evidence from human[12 13] and experimental[14] corneal transplantation, indicating a role for antibody in rejection: the allogeneic response may have been initiated by the host antibody response in days postvaccination and antibody may have been involved in graft injury.

SARS-CoV-2 is a novel virus to humans, in relationship to which the immune response and the long-term protective effects of vaccination remain unknown. The recent finding on the expression of multiple viral entry factors on human cornea[15] and reports of primary COVID-19 infection being temporally associated with rejection may offer insight into future understanding of interactions between SARS-CoV-2, the associated host immune response and the eye.[16 17] The BNT162b2 is a lipid nanoparticle-encapsulated mRNA molecule encoding a membrane-anchored SARS-CoV-2 full-length spike protein,[18] one of the vaccines based on mRNA which are being used for the first time in the SARS-CoV-2 pandemic. Data from vaccine trials confirm that the BNT162b2 vaccine generates both adaptive humoral and cellular immune responses in humans: elevation of antispike neutralising antibody titres were found in all subjects by day 21 following vaccination, antigen-specific CD4+ and CD8+ T cell responses, and levels of proinflammatory cytokines such as interferon gamma (IFNγ).[19 20] IFNγ-producing CD4+ T helper 1 (Th1) cells are thought to be a key cell type in corneal allograft rejection,[21 22] and cross-reactivity of virus antigen-specific T cells with the HLA antigen-disparate corneal allograft endothelial cells may be one driver for the rejection in the reported cases. Of note, a recent study into COVID-19 vaccine response in 187 solid organ transplant recipients—half of whom had the BNT162b2 vaccine—did not report any episodes of acute rejection.[23] Little is known about the biodistribution of lipid nanoparticles, a factor which may be relevant in the two patients reported since tissue trafficking of the mRNA would determine whether the cells and tissues in the eye are killed by cytotoxic T cells. Given the rapid uptake of vaccine proteins throughout the body, it would be anticipated that any significant upregulation of the immune response due to RNA-driven protein expression would occur within the first weeks, as seen in published data from completed trials, allowing us to promptly identify if rejection might occur at increased rates after vaccination.

Patients with corneal transplants and their clinicians should not be deterred from COVID-19 vaccination based on this report, and should note that both patients responded well to topical steroid treatment. Our aim is to highlight a potential consequence of immunogenicity of the mRNA vaccine, which may be shared with other types of SARS-CoV-2 vaccines and is likely to increase risk of rejection of all corneal transplant types. Early identification and management of graft rejection is important to prevent graft failure. A recent survey of 142 corneal surgeons reported 26.2% would increase the frequency of topical steroid when faced with vaccination-elicited rejection, but there was no consensus on rejection prophylaxis postvaccination.[24] More incidence data are needed before routine consideration of prophylactic steroid use immediately postvaccination. Clinicians may wish to consider such a strategy particularly in high rejection risk patients, and consider changing the frequency of existing steroid regimens or avoiding reduction in treatment around the time of planned vaccination. Delaying non-urgent keratoplasties in unvaccinated patients to allow them to undergo immunisation prior to surgery may be a worthwhile strategy. A recent vaccination history should be questioned when reviewing patients with signs of transplant rejection and any temporal association reported to the relevant local agencies.

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