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Complete List of Authors:	Phylactou, Maria; Moorfields Eye Hospital NHS Foundation Trust, Cornea and External Diseases Li, Ji-Peng; Moorfields Eye Hospital NHS Foundation Trust, Cornea and External Diseases Larkin, Daniel ; Moorfields Eye Hospital NHS Foundation Trust, Cornea and External Diseases
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Characteristics of endothelial corneal transplant rejection following immunisation with SARS-CoV-2 messenger RNA vaccine

Authors:

Maria Phylactou, MD, MSc, FEBO[1], Ji-Peng Olivia Li, MA (Cantab), FRCOphth[1], Daniel F P Larkin, MD, FRCOphth[1,2,3]

Affiliations:

[1]Cornea and External Diseases Service, Moorfields Eye Hospital, London, United Kingdom

[2]NIHR Moorfields Clinical Research Facility, Moorfields Eye Hospital, London, United Kingdom

[3]UCL Institute of Ophthalmology, London, United Kingdom

Corresponding author:

Maria Phylactou MD, MSc, FEBO

Moorfields Eye Hospital, 162 City Road, London, EC1V 2PD, United Kingdom

phylactou.maria@gmail.com

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SYNOPSIS

Acute DMEK allograft rejection was found in two patients at one and three weeks following SARS-CoV-2 mRNA vaccination. Rejection signs responded to intensive topical corticosteroid treatment. Recent vaccination history should be questioned in patients with corneal allograft rejection.

ABSTRACT

Aim

We report two cases of endothelial corneal allograft rejection following immunisation with SARS-CoV-2 mRNA vaccine BNT162b2 and describe the implications for management of transplant recipients post-vaccination for COVID-19.

Methods

A 66-year-old female with Fuchs endothelial 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 female with bilateral DMEK transplants for FECD three and six years earlier developed simultaneous acute endothelial rejection in both eyes, three 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 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 female, all findings were satisfactory at post-surgery examinations on days 2 and 7. These included full graft attachment, restoration of corneal transparency, central corneal thickness 525µm and best corrected visual acuity (BCVA) 6/6. Scheduled treatment was continued with topical dexamethasone 0.1% two-hourly for the first two weeks following surgery, then reduced to four times daily. The patient received the first dose of SARS-CoV-2 mRNA vaccine BNT162b2 (Pfizer-BioNTech, GmbH) at day 14 post-transplant. She presented with acute onset of blurred vision, redness and photophobia in the right eye seven days post-vaccination, at 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 mmHg. 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 IOL (Figure 1A). The left eye was uninflamed with minimal corneal oedema secondary to FECD and early cataract. Dilated fundoscopy was normal in both eyes. Anterior segment optical coherence tomography (AS-OCT) (MS-39, CSO, Florence, Italy) confirmed full graft attachment and central corneal thickness (CCT) of 652µm, which was significantly increased compared to 525µm on earlier post-transplant review on day 7 (Figures 1 C-D). An anterior chamber sample was examined for any possible associated virus-induced corneal inflammation: polymerase chain reaction with primers for cytomegalovirus, herpes simplex virus and varicella zoster virus was negative. As clinical appearances were typical of acute endothelial graft rejection, topical steroid frequency 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 6/6 7 days after presentation (Figures 1 B and E). Topical dexamethasone frequency was reduced to 2 hourly for 7 days and thereafter continued 4 times daily according to our standard endothelial keratoplasty protocol. At the latest examination four weeks post-rejection onset, visual acuity was good and there was no active inflammation.

CASE 2

An 83-year-old Caucasian female presented with sudden onset of bilateral blurred vision, pain, photophobia and redness. She underwent DMEK and cataract surgery for FECD in the right eye six years earlier, and the same procedure in the left eye three years earlier with replacement of an earlier DSEK graft. At the last examination five

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, GmbH) at 2 months (first dose) and 3 weeks (second dose) prior to the onset of symptoms.

At presentation, BCVA was 6/24 right and 6/12 left. 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 fundoscopy was normal in both eyes. CCT was 660µm OD and 622µm 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 BCVA in both eyes. 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 (PK) in high rejection risk eyes. The effector response in endothelial rejection is characterised by anterior chamber 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).

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

Study	Patient Age/Laterality	Eye/Episode	Vaccine	Interval post-graft	Type of graft	Interval post-vaccine	Outcome
Solomon and Frucht-Pery 1996	**Patient (1)** 80 Bilateral, Simultaneous	OD/first	Influenza (trivalent vaccine for the inactivated strains of A-Beijing-32/92-H3N2, A-Texas-36/91-HINI, and B-Panama-45/90 of the influenza virus)	11 years	PK	6 weeks	Resolved with topical and subtenons steroids and systemic steroids (80mg prednisolone orally per day)
		OS/first	Influenza (trivalent vaccine for the inactivated strains of A-Beijing-32/92-H3N2, A-Texas-36/91-HINI, and B-Panama-45/90 of the influenza virus)	8 years	PK	6 weeks and 3 days	Resolved with topical and subtenons steroids and systemic steroids (80mg prednisolone orally per day)
Wertheim et al. 2006	**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. 2015	**Patient (4)** 33 Unilateral	OD/first	Influenza Fluvax, CSL, Parkville, VIC, 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
Vignapiao et al. 2021	**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, DMEK: Descemet's membrane endothelial keratoplasty, PK: Penetrating keratoplasty

Whilst 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 EK 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 anterior chamber[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 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 post-vaccination and antibody may have been involved in graft injury.

The SARS-CoV-2 virus 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 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 in 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 anti-spike neutralising antibody titres were found in all subjects by day 21 following vaccination, antigen-specific CD4+ and CD8+ T-cell responses, and levels of pro-inflammatory cytokines such as IFNγ[19-20]. IFNγ-producing CD4+ 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 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 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 the

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 post-vaccination[24]. More incidence data are needed before routine consideration of prophylactic steroid use immediately post-vaccination. 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 transplant rejection signs and any temporal association reported to the relevant local agencies.

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Contributorship statement: MP, JPOL and DFPL conceived the study and wrote the manuscript. MP and JPOL collected the clinical data. All authors read and approved the manuscript.

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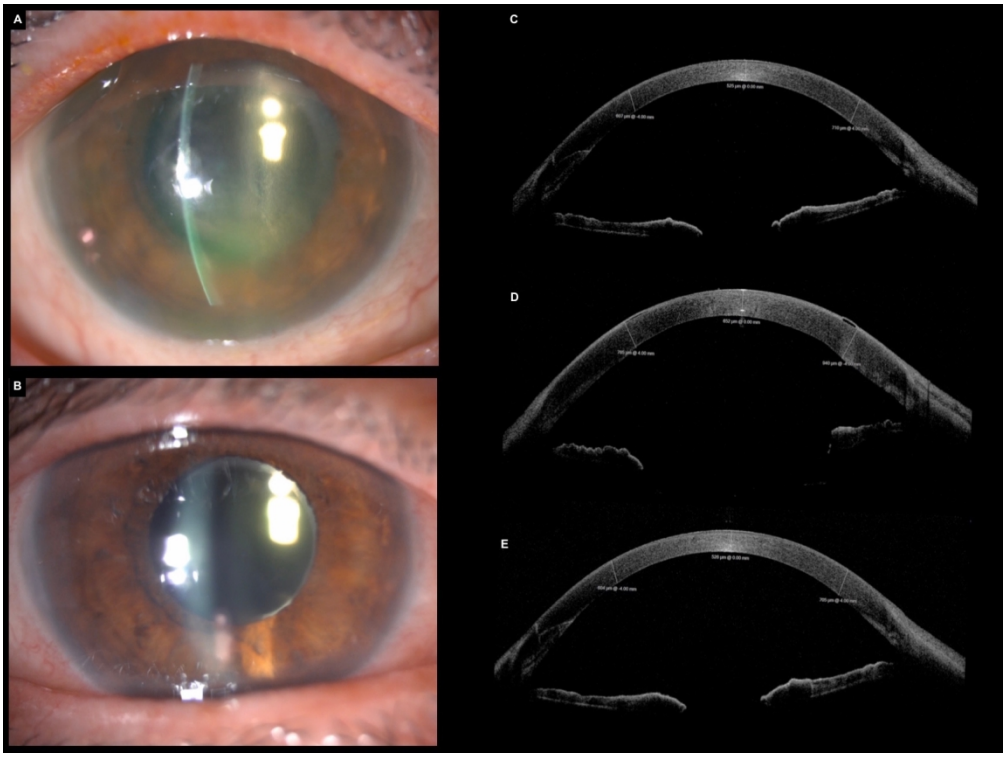
FIGURE LEGENDS

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

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

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 arrowheads) images; attached bright cells with extending processes attached to donor corneal endothelial cells (arrows) on *in vivo* confocal microscopy (D). Corresponding images of left cornea (E-H).



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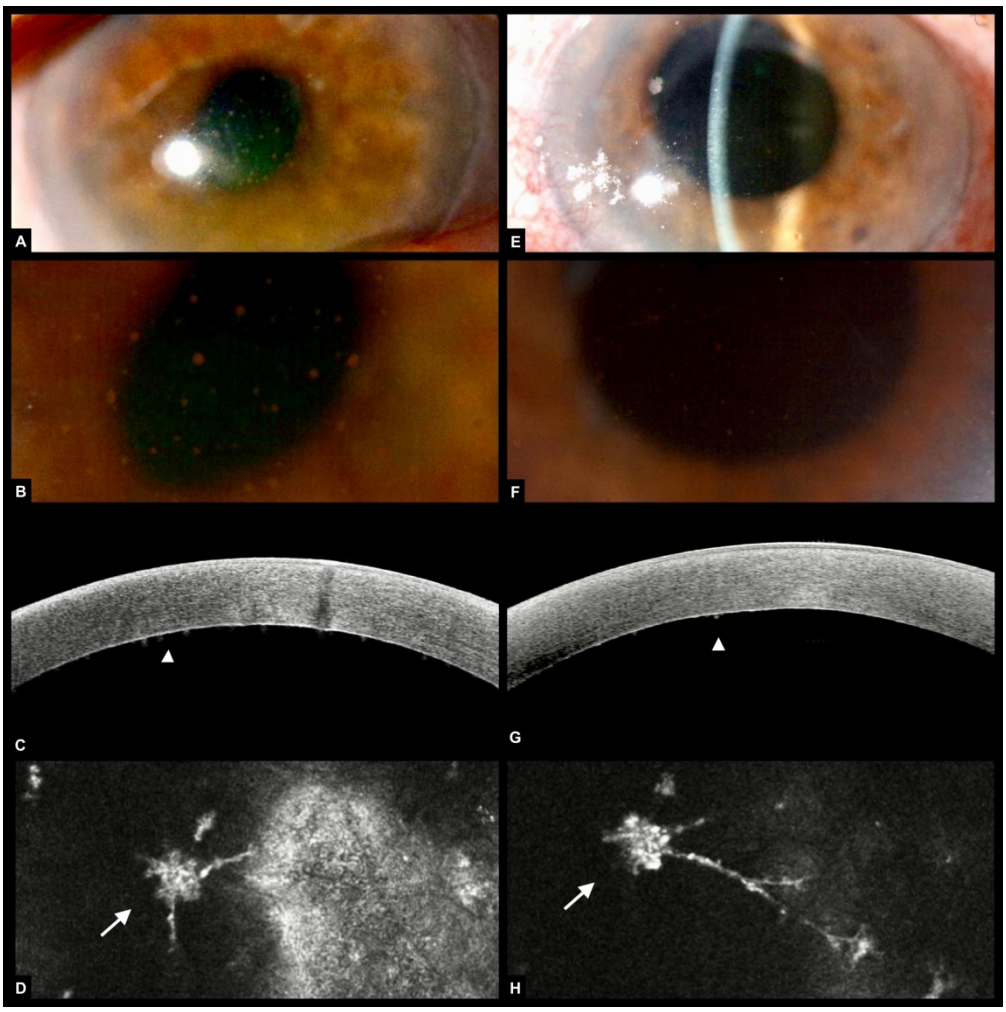

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