*Case report*

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# Acute corneal graft rejection after anti-severe acute respiratory syndrome-coronavirus-2 vaccination: A report of four cases

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## Abstract

**Purpose:** This study intends to add to previous reports on acute corneal graft rejection following anti-severe acute respiratory syndrome-coronavirus-2 vaccination, providing data to corroborate a possible causative relationship between anti-COVID-19 immunization and corneal graft rejection, regardless of vaccine or graft type.

**Methods and Results:** This report describes 4 cases of acute-onset rejection as early as 5 days following the first dose of anti-severe acute respiratory syndrome-coronavirus-2 vaccine types not yet referred for corneal allograft. Patients were individually given the Moderna messenger RNA-1273 COVID-19 vaccine (2 patients) and the AstraZeneca COVID-19 vaccine, Vaxzevria, AZD1222 (2 patients).

**Conclusions:** Even though a direct causative effect is hard to prove, temporal proximity between anti-severe acute respiratory syndrome-coronavirus-2 vaccines of different types and consecutive reports of corneal graft rejection indicates the need for further investigation. Consistent advice must be given to corneal transplant patients regarding such risk.

## Keywords

Cornea, graft, rejection, vaccination, anti-severe acute respiratory syndrome-coronavirus-2, COVID-19

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## Introduction

Over the past couple of decades, corneal grafting has progressed from previously exclusive penetrating keratoplasty (PK) to lamellar procedures with a significantly lower risk of graft rejection.

Since early 2020, when severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was declared a pandemic, the world has been facing an ongoing battle entailing completely new immunologic implications. Nations and pharmaceutical companies have come together to minimize SARS-CoV-2 morbidity and mortality by developing several immunization models: messenger RNA (mRNA), DNA-based, inactivated virus, and others. Since the immunity to COVID-19 may only be temporary, mass vaccination is being used to achieve so-called "herd immunity,"[1] with different vaccines being given to more and more individuals, including those with corneal and other organ transplants.

This report follows on the articles by Wasser et al.[2] in May 2021 and by Phylactou et al.[3] in April 2021 that

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cited 4 other cases of post-COVID-19 immunization corneal transplant rejection, all of which related to the SARS-CoV-2 mRNA vaccine BNT162b2 (Pfizer-BioNTech), and a recent report (July 2021) related to the virus vector vaccine ChAdO × 1 nCoV-19 Corona Virus Vaccine Recombinant (COVISHIELD™).[4] We identified 2 cases of graft rejection following the AstraZeneca COVID-19 vaccine, Vaxzevria (AZD1222) —one of which occurred as early as 5 days after the first dose—and 2 cases following the Moderna mRNA-1273 COVID-19 vaccine.

Given the chronological proximity indicated by our own data and the data provided by the previous studies, we suspect there may be a direct correlation between anti-COVID-19 vaccination, regardless of vaccine type, and corneal allograft rejection, regardless of vaccine or graft type. Immune-mediated mechanisms triggered by immunization may be responsible for the ocular inflammatory reaction experienced by these patients.

## Description of the cases

### *Patient I*

A 77-year-old Caucasian woman was referred for Descemet's membrane endothelial keratoplasty (DMEK) on the left eye (LE) due to pseudophakic bullous keratopathy 20 months before our study. The eye had undergone phacoemulsification with intraocular lens (IOL) implantation 14 months prior to transplantation. The fellow eye had Fuch's endothelial corneal dystrophy (FECD), in addition to a hyperdense nuclear cataract, but it was kept under observation until stability in the LE could be achieved. During the 20-month post-grafting follow-up, the patient presented signs of graft rejection on 3 different occasions, indicated by keratic precipitates (KPs) and stromal edema. Two of the episodes were concomitant with herpes simplex keratitis and were thus attributable to viral reactivation. Proper antiviral medication was included in the drug regimen, resulting in a prompt positive response. There were no other comorbidities. The third episode, 8 months after grafting, was unresponsive to intensive topical and systemic corticotherapy (1 mg/ml dexamethasone eye drops and injectable solution) plus antiviral cover (valacyclovir); consequently, regrafting was conducted (Figure 1. 1(a)). The patient was kept on the same topical corticosteroid drops and oral antiviral medication, despite a negative anterior chamber polymerase chain reaction for the Herpes simplex virus. The outcome was that the cornea was clearer than it ever had been during the 12 months of regraft. However, that changed after she received the first dose of the Moderna anti-SARS-CoV-2 vaccine in accordance with the corresponding age group schedule, as determined by Greece's national vaccination campaign against the COVID-19 pandemic. One week after receiving the vaccine, she noticed blurred vision in the LE. She was expeditiously brought in for an examination, which revealed subtle corneal edema and small pigmented KPs (Figure 1. 1(b)). Subconjunctival dexamethasone was administered, and the topical corticosteroid formulation was adjusted to every 2 h, in addition to hypertonic eye drops. Six days later, the edema had worsened, with subepithelial bullae, suggesting an active rejection process (Figure 1. 1(c)). Intravenous dexamethasone was administered, and the topical corticosteroid was switched to on-the-hour application. Four weeks after onset, the eye had calmed down and the edema had started to fade (Figure 1. 1(d)).

### *Patient II*

A 64-year-old Caucasian woman was subjected to repeated PK on the right eye (RE) in December 2018 due to failure of the initial corneal graft for keratoconus (2002). The eye was pseudophakic before regrafting. The transplant has been clear for 2 years after surgery (Figure 1. 2(a)), with a central corneal thickness (CCT) of 470 μm (Figure 1. 2(b)). Corrected distance visual acuity (CDVA) was 8 of 10 with glasses and 10 of 10 with contact lenses. Three months prior to our study, the patient had received the first dose of Moderna's anti-SARS-CoV-2 vaccine, followed by the second dose 4 weeks later. The patient experienced gradual deterioration of vision in her RE 1 week after the second dose and she came to the clinic 3 days later. Slit-lamp examination revealed diffuse corneal edema, which was more pronounced on the nasal side of the graft (Figure 1. 2(c)), as well as cells (+) in the anterior chamber. Corneal thickness was 585 μm on the apex of the graft and 680 μm on the nasal side (Figure 1. 2(d)). CDVA had decreased to 2 of 10. Despite intensive, hourly treatment with corticosteroid drops (dexamethasone) and intracameral corticosteroid injection (fortecortin), the corneal edema persisted, particularly on the nasal side of the graft, 4 weeks after the beginning of therapy.

### *Patient III*

A 69-year-old Caucasian man was referred for PK on the RE 2 years prior to our study. The patient had type 2 diabetes managed with insulin. The eye was pseudophakic and had been treated for diabetic macular edema with an intravitreal dexamethasone implant. Severe herpetic keratitis ensued after the intraocular procedures, resulting in extensive post-herpetic corneal scarring (Figure 2. 3(a)). Corneal grafting was carried out 18 months later (Figure 2. 3(b)). Due to his history of herpes, the patient was kept under permanent antiviral cover with valacyclovir. The LE had been treated for diabetic maculopathy with intravitreal injections of bevacizumab and had undergone uneventful phacoemulsification with IOL

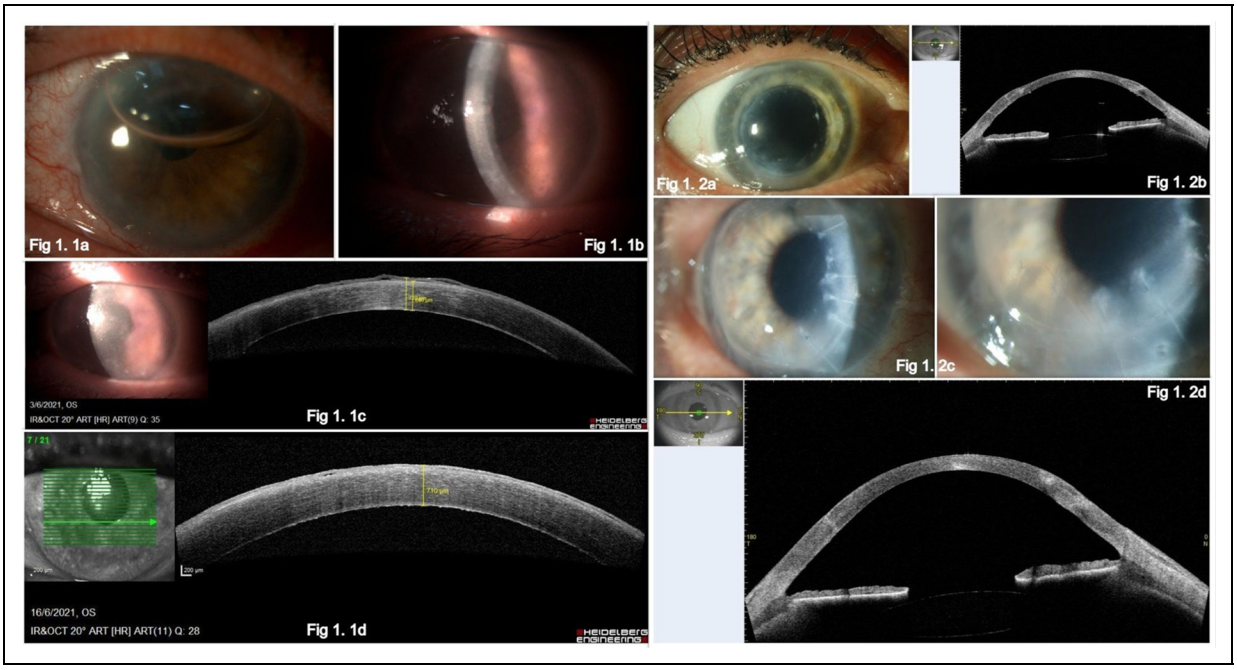


**Figure 1.** Patients I and II (Moderna vaccine). Patient I. **1a**: Slit-lamp photograph of the LE at first-day post-DMEK, showing a relatively calm eye, with virtually no corneal edema. **1b**: Slit-lamp photograph displaying initial corneal edema and pigmented KPs. **1c**: Slit-lamp photograph and anterior OCT of the LE showing worsening corneal edema and subepithelial bullae. CCT is 720 μm, 650 μm of which corresponds to the stroma. **1d**: Clearing edema, absorption of bullae, and improvement of CCT to 710. Patient II. **2a**: Wide beam slit-lamp photograph of the RE displaying a clear corneal graft. **2b**: Anterior OCT showing a thin graft with CCT of 470 μm. **2c**: Slit-lamp photograph revealing corneal edema, more pronounced on the nasal side of the graft. **2d**: Increased corneal thickness in contrast with previous OCT, indicating diffuse corneal edema.
CCT: central corneal thickness; KPs: keratic precipitates; LE: left eye; OCT: optical coherence tomography; RE: right eye;

implantation. The graft had an excellent outcome (Figure 2. 3(c)) and was clear for 22 months, until the patient received the first dose of the AZD1222, as per the vaccination program in the patient's country, Albania. Five days later, the patient noticed a decrease in visual acuity in his RE. Ophthalmologic examination revealed diffuse corneal edema and KPs (Figure 2. 3(d)). A course of 4 subconjunctival dexamethasone injections was administered. A combined oral (methylprednisolone) and topical (dexamethasone) corticotherapy was initiated, resulting in the cessation of the anterior chamber reaction, although marked stromal edema persisted after 4 weeks of treatment (Figure 2. 3(e)). A significant reduction of corneal thickness was achieved after 8 weeks of treatment, with a measurement of 660 μm at the thinnest point (Figure 2. 3(f)).

### *Patient IV*

A 63-year-old Caucasian man had undergone a second Descemet stripping endothelial keratoplasty (DSAEK) on the LE for FECD a year earlier. The eye was pseudophakic, with a posterior chamber IOL, having undergone uneventful phacoemulsification. The first endothelial graft never functioned properly and was replaced after 4 months. The second graft was clear for 9 months until the patient was given AZD1222. Ten days after the first dose, he developed acute allograft rejection manifested as blurred vision and corneal edema (Figure 2. 4(a) and 4(b)). Upon emergency examination, his CDVA had dropped from the previous 5 of 10 to finger count at 1 m and CCT was 850 μm. The frequency of the use of dexamethasone drops was increased from once daily to every 2 h and a hypertonic ointment was added to the therapy regimen. Nevertheless, no substantial change was noticeable after 3 weeks of follow-up.

## Discussion

The cornea is the most frequently transplanted tissue in the human body. The primary cause of corneal graft failure is immune rejection, a highly complex sequence of immune responses that promote tissue destruction. Anterior chamber reaction and KPs are common signs of graft rejection. Vaccinations have been indicated as possible triggers for corneal graft rejection, although prior rejection episodes still seem to be the most relevant. The immune response to vaccination can induce major

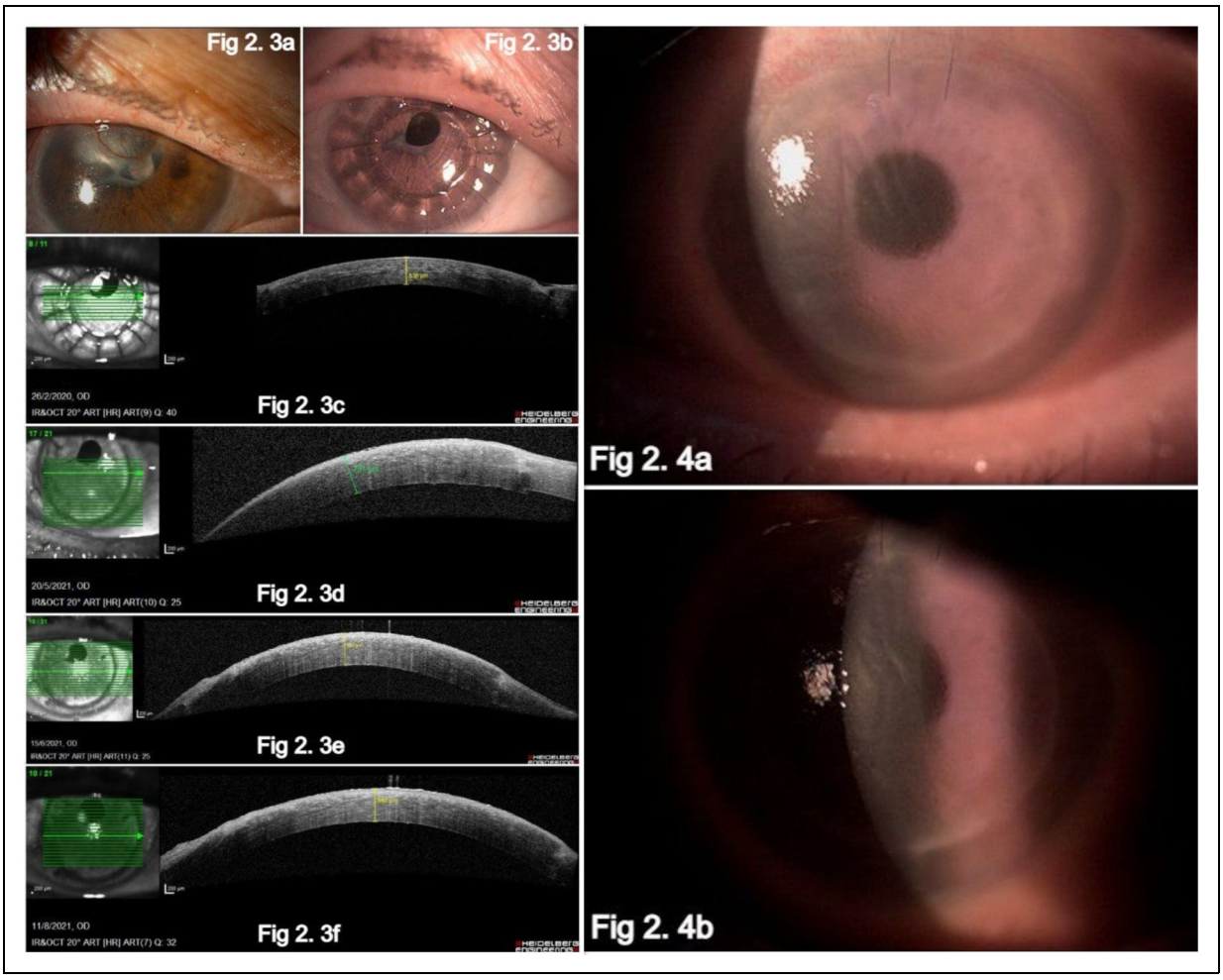


**Figure 2.** Patients III and IV (AstraZeneca vaccine). Patient III. **3a**: Slit-lamp photographs of the RE, depicting deep superior post-herpetic corneal scarring, extending to the visual axis. **3b**: PK postoperative aspect. **3c**: Anterior OCT at 8 months after a corneal transplant, outlining a regular graft with CCT of 535 μm. **3d**: Slit-lamp photograph and OCT at the onset of the rejection episode, revealing anterior chamber reaction and diffuse graft edema. Notice subepithelial bullae and CCT of 757 microns. **3e**: At 4 weeks of treatment, CCT is still 802 μm, despite a calmer anterior chamber. **3f**: Two months later, CCT is down to 660 μm. Patient IV. **4a**: Wide beam slit-lamp photograph of the LE after DSAEK, showing diffuse corneal edema, Descemet folds, and keratic precipitates. **4b**: Signs best evidenced under narrower beam illumination.
CCT: central corneal thickness; LE: left eye; OCT: optical coherence tomography; PK: penetrating keratoplasty; RE: right eye.

histocompatibility complex class II complex antigens in all layers of the grafted cornea,[4] which can explain the susceptibility of different graft types regardless of grafting technique.

For most viral infections, vaccination is directed at promoting cellular and humoral immunity in the uninfected population.[5] The anti-COVID-19 vaccines currently in use differ in their immunization mechanism, based on their antigenic design. Both AZD1222 and COVISHIELD™ are non-replicating viral vector vaccines employing an Adenovirus (common cold-causing virus with a DNA genome) derived from chimpanzees. Viral vectors have the property of entering dendritic cells, leading to enhanced antigen presentation and immune cell activation. However, viral vectors may also lead to widespread tissue tropism, inducing severe side effects.[1] The Moderna vaccine acts in the same way as the Pfizer-BioNTech vaccine, its counterpart mRNA vaccine, a new generation of vaccines that use nanotechnology to encode the virus-binding protein, inducing neutralizing antibodies into the angiotensin-converting enzyme 2 receptors, expressed in virtually all organs.

Acute corneal transplant rejection had already been reported in concomitance with COVID-19 disease. In 2020, Singh and Mathur[6] reported a case of full-blown acute rejection during SARS-CoV-2 infection. The patient had 6 years of clear graft after combined PK and phacoemulsification with posterior chamber IOL for post-

traumatic corneal leukoma and cataract.[6] Jin and Juthani[7] published the occurrence of acute endothelial rejection coinciding with COVID-19 infection, 3 months after an uncomplicated PK for keratoconus.[7] It is possible that the inflammatory storm triggered by COVID-19 infection overcomes corneal immune privilege, giving rise to allograft rejection episodes. On a lower scale, the same pathway may lead to the inflammatory immune response triggered by vaccination.

The issue of vaccine-associated corneal graft rejection risk is neither a novelty nor an exclusivity of COVID-19. In a 2020 survey assessing cornea specialists' decision-making regarding herpes zoster and influenza vaccines in all keratoplasty scenarios, 19.7% stated that they had clinical experience with a vaccine-associated rejection episode.[8] Corneal allograft rejection has also been reported following other types of immunization, such as influenza, hepatitis B, tetanus, and yellow fever,[9] even in the setting of deep anterior lamellar keratoplasty. The bilateral simultaneous occurrence of graft rejection after influenza immunization confirmed the direct causal association. Medical advice and management of graft patients in the light of vaccination, however, is still largely based on individual physician judgment, pending prospective research for the issuance of evidence-based guidelines.[8] For instance, specific recommendations regarding intervals of multi-dose vaccines—as is the case with most anti-COVID-19 vaccine regimens—in the setting of graft or graft rejection, are lacking.

Acute allograft rejection following immunization with Pfizer-BioNTech—kidney transplant—and Moderna—liver transplant—has also been reported regarding previously favorable outcomes. Recipients of immunosuppressive medications were excluded from the trials of both vaccines, a fact that adds to the obscurity around their immune-related side effects.[10]

Topical corticosteroids are the mainstay of corneal graft rejection management. In higher-risk situations, systemic corticosteroids and/or immunosuppressive drugs may be of benefit. If diagnosed early, corneal transplant rejection can be reversed, although there may be endothelial cell loss. Given the distress and potential threat to vision brought about by rejection episodes, patients should be informed of this potential risk and warned of its symptoms before receiving anti-SARS-CoV-2 vaccination.

## Ethical approval

This study was approved by the Institutional Review Board of the Ophthalmica Eye Institute, in Thessaloniki, Greece. Appropriate written patients' consent to publish was obtained.

## Author Contributions

MB, DM, ZG, and PBP contributed to the study's conception and design, image acquisition, text writing, and bibliography search. GS and VV contributed by critically revising the manuscript for important intellectual content. All the authors are responsible for the final approval of the version to be published and agree to be accountable for all aspects related to the accuracy or integrity of the reported cases.

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