ECRONICON OPEN ACCESS

EC OPHTHALMOLOGY
Case Report

Keratoplasty, Immunosuppressors and SARS-CoV-19

Victoria Myasnikova[1]*, Sergey Sakhnov[1], Denis Nefedov[1], Ekaterina Afonina[1], Tamriko Zakaraiia[2] and Shu Ruset[1]

[1]*Krasnodar Branch of the S.N. Fedorov NMRC MNTK Eye Microsurgery, Krasnodar, Russia*

[2]*Saint-Petersburg Branch of the S.N. Fedorov NMRC MNTK Eye Microsurgery, Saint-Petersburg, Russia*

***Corresponding Author:** Victoria Myasnikova, Krasnodar Branch of the S.N. Fedorov NMRC MNTK Eye Microsurgery, Krasnodar, Krasnodarskiy Kray, Russia.

Received: January 31, 2023; **Published:** February 22, 2023

Abstract

We report a case of a successful outcome of keratoplasty in a keratoconus patient with an episode of coronavirus disease 2019 (COVID-19) in the postoperative period.

Keywords: *Keratoconus Corneal Transplantation; SARS-CoV; Immunosuppressants Graft Rejection; COVID-19 Pandemic*

Introduction

The ongoing SARS-CoV-19 pandemic has affected all areas of ophthalmic care, especially keratoplasty. In many countries, a sharp decrease in the number of donated corneas has led to a reduction in transplants, to the point of stopping them altogether. A statistical report by the Eye Bankers Association of America (EBAA) showed that due to the COVID-19 pandemic and the moratorium on elective surgery, both the number of tissue donations (-20.4%) and transplants (-8.8%) declined in 2020 [1]. This is in no small part due to the fact that the presence of coronavirus-2 RNA in human corneal tissue and the risk of transmission of COVID-19 to the recipient has become a highly topical issue [2].

In addition, information has emerged about the effect of coronavirus infection sustained in the postoperative period of keratoplasty on graft engraftment. Although the cornea is an immune-privileged organ, allogeneic graft rejection is a frequent complication of keratoplasty: according to Barraquer RI., *et al.* (2019) the 10-year survival rate is 95% in patients with keratoconus and 55 to 14% in high-risk keratoplasty [3]. Coronavirus infection has corrected the current reality and may have become an additional risk factor for corneal graft rejection. Current published clinical cases have demonstrated the ability of SARS-CoV-2 infection, either postoperatively or by vaccination with SARS-CoV-2 RNA, to induce corneal graft rejection [4-6].

The use of immunosuppressive drugs administered to reduce the risk of allogeneic graft rejection remains controversial due to their possible effect on the severity of the covid infection [7].

We report a case of penetrating keratoplasty performed in a keratoconus patient followed by development of coronavirus 2019 (COVID-19) and a favourable outcome in the form of transparent graft engraftment at 12 months follow-up.

Case Presentation

The clinical case was followed at The S Fyodorov Eye Microsurgery Federal State Institution, Krasnodar Branch, Russia.

A 35-year-old Caucasian woman first came to the clinic in September 2019 with complaints of permanently deteriorating vision. Diagnosis was carried out and the results were as follows:

- Refractometry and visometry:
  - Vis OD 0.01 sph -2.50 cyl -2.50 Ax 60 = 0.15 (20/135)
  - Vis OS count 20 cm sph - 17.75 cyl - 4.75 Ax 23 = 0.06 (20/400)
- Keratometry: OD - K1 57.5D K2 59.5 D, OS - K1 59.5D K2 69.62 D
- Pachymetry: The minimal corneal thickness of OD was 422 μm; the minimal corneal thickness was 392 μm. The endothelial cell density of 1900 cells/mm^2. The Schirmer test was particularly alarming: OD 2 mm, OS 6 mm.

The patient was diagnosed with grade 3 bilateral keratoconus and Dry Eye Disease (DED). Sjögren's syndrome was excluded during a consultation with a rheumatologist. The following therapy was prescribed: Cyclosporine A (topically) 2 times a day for 6 months as a treatment for SSI, moisturising drops - hyaluronic acid sodium salt - 6 times a day, scheduled keratoplasty on the left eye.

A penetrating keratoplasty was performed in the left eye using a Ziemer Z8 femtosecond laser (Switzerland) on 6.02.2020. Characteristics of the donor material: material from 03.02.2020, transplantability index - 3 "A", PEC (endothelial cell density) - 3436.

The graft was fixed with continuous sutures. Epithelialization of the graft occurred on day 4. The patient was discharged home with topical antibiotics, corticosteroids, reparative drugs and Cyclosporin A (CSA) twice daily for 5.5 months. The patient had an uncomplicated operative and early postoperative course with no signs of graft rejection.

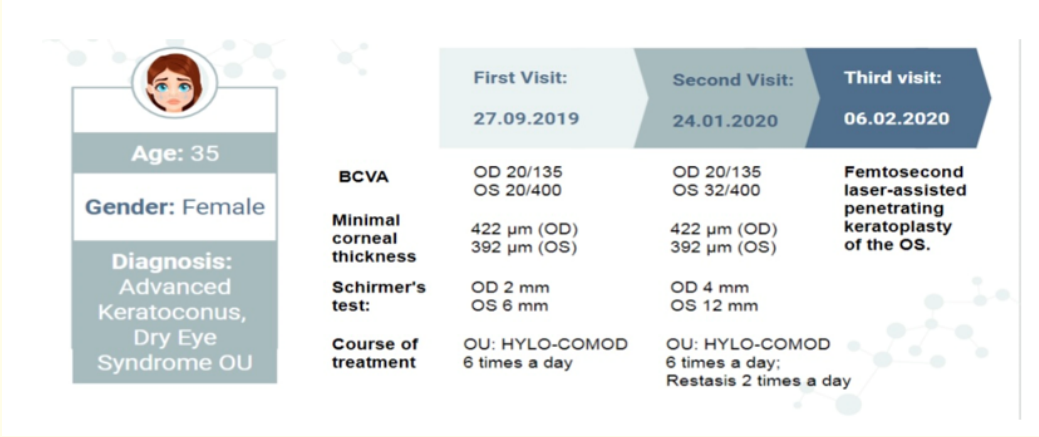

Figure 1

Three months after keratoplasty, the patient was admitted to a hospital on 16.05.2020 with SARS-CoV-2019 multisegmental pneumonia and persistent hyperthermia. Laboratory tests revealed neutropenia and thrombocytopenia, PCR test for SARS-CoV-2019 RNA was positive. Therapy included antiviral, antipyretic drugs and antibiotics.

The following ophthalmological complaints were present: reddening of the conjunctiva, scratchy pain, decreased vision and a sensation of shading. Due to quarantine and inability to get an ophthalmologist consultation at the clinic, a telemedicine consultation with The S. Fyodorov Eye Microsurgery Federal State Institution was organised, during which the appropriate treatment was prescribed: Oftalmoferon, Vitabact, Broxinac, CSA. After seven days, the ophthalmological symptoms had resolved and recovery was achieved. Thirteen days after admission the patient was discharged from the covid unit.

Presented at follow-up examination on 02.07.2020: left eye was normal, no discharge, graft was clear, epithelialized, suture was intact, anterior chamber depth was 3 mm, iris was not discolored, lens was clear. A contact lens was fitted in the right eye, the left eye continues treatment according to the standard regimen. BCVA was 27/135 on the right eye and 20/135 on the left eye.

On 03.12.2020, at the next visit, the following parameters were revealed: BCVA of the right eye was 20/135 and BCVA of the left eye was 41/135; minimum corneal thickness was 440 μm in the right and 434 μm in the left eye, endothelial cell density (cells/mm) of the OD 2425 cells/mm^2, OS 2579 cells/mm^2.

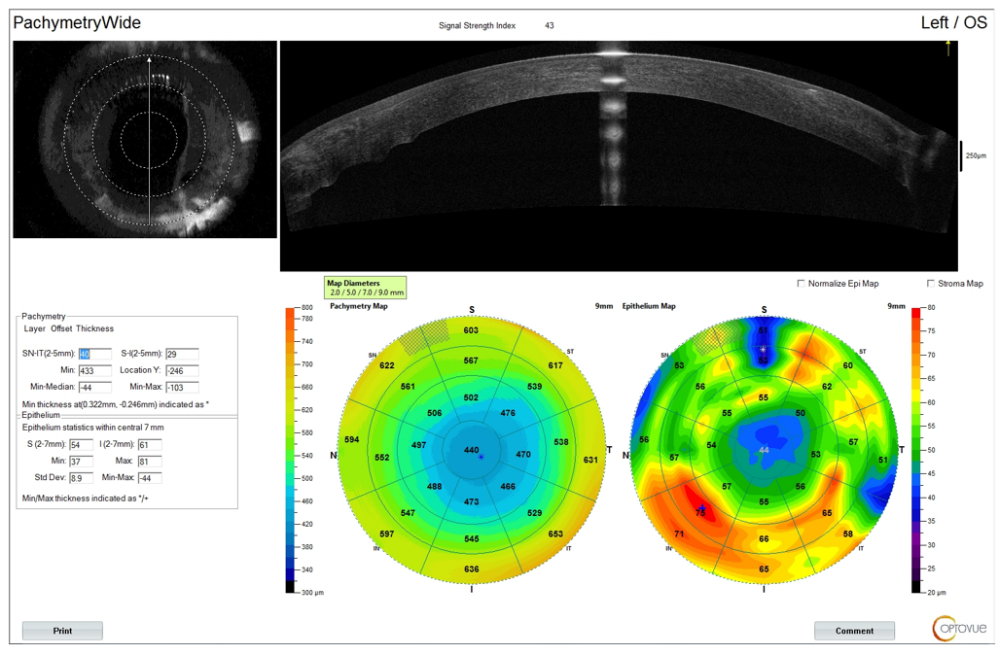

Figure 2

Examination results 12 months after keratoplasty (08.02.2021): BCVA of 81/135 in the left eye, transparency of the graft and absence of inflammatory reactions, allow us to state that keratoconus treatment results are quite successful: from preoperative BCVA 20/400 to BCVA 81/135.

Discussion

We reviewed current publications describing patients who have undergone keratoplasty and subsequent coronavirus infection, as well as those who were immunised against COVID-19 following corneal transplantation. A recent case report by Jin SX., *et al*. (2021), illustrated

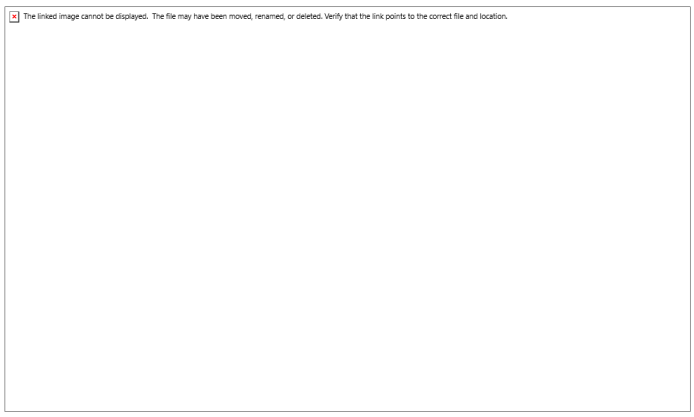

Figure 3

acute corneal endothelial graft rejection that developed concomitantly with concomitant COVID-19 infection. The authors suggested that COVID-19 infection may lead to a weakening of the ocular immune system, contributing to corneal graft rejection [4]. An article published by Maria Phylactou., *et al*. (2021) presented two clinical cases of corneal endothelial allograft rejection following immunisation with the SARS-CoV-2 vaccine with BNT162b2 messenger RNA (mRNA). The authors hypothesise that the allogeneic response may have been initiated by a host antibody response after vaccination and notify of the possibility of corneal graft rejection associated with vaccine administration, suggesting that vaccination of patients before elective keratoplasty should be considered [5]. A case report published by Singh., *et al*. (2021) describes an episode of acute graft rejection coinciding with COVID-19 disease in a 32-year-old man after a penetrating keratoplasty performed 6 years ago. The authors emphasise that the rejection symptoms developed during the cytokine storm phase, as evidenced by elevated inflammatory markers in blood tests [6].

All of the publications we found documented graft rejection in the outcome of covid disease in the recipient and suggest a causal relationship between these two phenomena.

In addition to assessing the effect of Coronavirus disease-2019 on graft engraftment, a relevant issue is the safety and efficacy of immunosuppressive therapy in the recipient. The treatment prescribed for our patient with CCS, in addition to tear replacement therapy, included CSA as an immunosuppressive agent. To substantiate the conclusions about the feasibility of immunosuppressive therapy in patients with transplanted corneas at risk of COVID-19 infection, we searched for publications using the keywords: keratoplasty, graft rejection reaction, immunosuppressors, SARS-CoV-19.

The mechanism of action of cyclosporine A is described in detail in a review by Periman LM., *et al*. published in 2020 [8]. CsA is a calcineurin inhibitor and has potent immunosuppressive activity by preventing infiltration, T-cell activation and subsequent release of IL-2 and IL-4. In addition, CsA reduces the expression of pro-inflammatory cytokines and chemokines IL-1β, TNF-α, IL-6, intercellular adhesion molecule 1 and MHC. CsA protects human conjunctival epithelial cells through its anti-apoptotic action, and also improves conjunctival bokal cell density and corneal surface integrity through its immunomodulatory activity [9].

In the context of the pandemic, ophthalmologists face another question: how does immunosuppressive therapy affect the severity of the course of COVID-19 in patients? A retrospective cohort study of over 2000 people showed that chronic use of immunosuppressive

drugs was associated with neither worse nor better clinical outcomes among adults hospitalised with COVID-19 in a US healthcare system [7]. Moreover, there is now encouraging evidence to suggest that immunosuppressants, with the exception of high-dose corticosteroids, play a positive role in the treatment of COVID-19 disease and, as a consequence, a patient with induced immunosuppression may, paradoxically, have a protective effect [10].

This information is consistent with the above data that CSA reduces the expression of the pro-inflammatory cytokines and chemokines IL-1β, TNF-α, IL-6, thus having the ability to suppress the cytokine storm [9]. Moreover, according to several authors, it is the cytokine storm that coincides with acute corneal allograft rejection [3,7].

Thus, taking into account the presented observation experience of this clinical case and the literature data, we assume that by prescribing immunosuppressive therapy and tear substitutes, we managed to avoid probable ocular complications in a patient with coronavirus disease developing in the postoperative period. It should be emphasised that the conjunctivitis caused by COVID-19 did not lead to rejection or opacification of the graft. In addition, timely correction of therapy by an expert ophthalmologist under quarantine conditions was organised through a system of telemedical consultations. Our observations are consistent with scientific studies of the mechanism of action of cyclosporine on immunity in COVID-19 disease.

Conclusion

This patient gives us the possibility to demonstrate clear graft engraftment and recovery from SARS-CoV-19, as well as the efficacy and safety of the immunosuppressive drug cyclosporine A in the perioperative period of keratoplasty in the Covid-19 era.

Conflict of Interest

The authors have declared that no financial interest or any conflict of interest exist.

Bibliography

1. Eye Bank Association of America. 2020 Eye Banking Statistical Report.

2. Casagrande M., *et al*. "Presence of SARS-CoV-2 RNA in the Cornea of Viremic Patients With COVID-19". *JAMA Ophthalmology* 139.4 (2021): 383-388.

3. Barraquer RI., *et al*. "Risk factors for graft failure after penetrating keratoplasty". *Medicine* 98.17 (2019): e15274.

4. Jin SX and Juthani VV. "Acute Corneal Endothelial Graft Rejection with Coinciding COVID-19 Infection". *Cornea* 40.1 (2021): 123-124.

5. Phylactou M., *et al*. "Characteristics of endothelial corneal transplant rejection following immunisation with SARS-CoV-2 messenger RNA vaccine". *British Journal of Ophthalmology* 105.7 (2021): 893-896.

6. Singh G and Mathur U. "Acute graft rejection in a COVID-19 patient". *Indian Journal of Ophthalmology* 69.4 (2021): 985-986.

7. Andersen KM., *et al*. "Association Between Chronic Use of Immunosuppresive Drugs and Clinical Outcomes From Coronavirus Disease 2019 (COVID-19) Hospitalization: A Retrospective Cohort Study in a Large US Health System". *Clinical Infectious Diseases* 73.11 (2021): ciaa1488.

8. Periman LM., *et al*. "A Review of the Mechanism of Action of Cyclosporine A: The Role of Cyclosporine A in Dry Eye Disease and Recent Formulation Developments". *Clinical Ophthalmology* 14 (2020): 4187-4200.

9. Utine CA., *et al*. "Clinical review: topical ophthalmic use of cyclosporin A". *Ocular Immunology and Inflammation* 18.5 (2010): 352-361.

10. Thng ZX., *et al*. "COVID-19 and immunosuppression: a review of current clinical experiences and implications for ophthalmology patients taking immunosuppressive drugs". *British Journal of Ophthalmology* 105.3 (2021): 306-310.

Volume 14 Issue 3 March 2023