

# Bilateral corneal endothelial failure following COVID-19 pneumonia

Li Jiang, Yit Yang, Jaishree Gandhewar

Ophthalmology, Wolverhampton Eye Infirmary, Wolverhampton, UK

Correspondence to  
Dr Li Jiang; li.jiang@nhs.net

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## SUMMARY

We describe a patient who developed acute bilateral corneal decompensation following COVID-19 pneumonia and prolonged intensive care unit ventilation. SARS-CoV-2 uses human ACE2 as the receptor for entry with subsequent downregulation of ACE2. ACE2 receptors are found in human ocular surface cells including cornea. Mouse models of ACE2 deficiency result in corneal haze, oedema and ocular surface inflammation due to upregulation of the inflammatory cascades. We therefore hypothesise that the cause of this patient's corneal decompensation was viral endotheliitis due to direct infection by the SARS-CoV-2 virus.

## BACKGROUND

SARS-CoV-2 has been detected in ocular secretions and ocular surface cells.<sup>1</sup> SARS-CoV-2 uses human ACE2 as the receptor for entry with subsequent downregulation of ACE2.<sup>2</sup> ACE2 receptors are found in human ocular surface cells including the cornea and there have been recent reports of conjunctivitis and keratoconjunctivitis in patients with COVID-19.<sup>3,4</sup> To date reported ocular findings resolve with medical treatment<sup>5</sup> and there are no reports of corneal decompensation and long-term effects on vision. We describe the first reported case of bilateral acute corneal decompensation following COVID-19 pneumonia and prolonged intensive care unit (ICU) ventilation. Mouse models of ACE2 deficiency result in corneal haze, oedema and ocular surface inflammation due to upregulation of the inflammatory cascades. We therefore hypothesise that the cause of this patient's corneal decompensation was viral endotheliitis due to direct infection by the SARS-CoV-2 virus.

## CASE PRESENTATION

A 58-year-old Caucasian man reported bilateral visual blurring following 34 days of prolonged ventilation on ICU for COVID-19 bronchopneumonia. Initial bedside examination showed hazy corneas and mild limbal injections, so a full eye examination was arranged. Best corrected visual acuities were 6/24 in the right eye, 6/9 in the left eye. Limbal conjunctiva was mildly injected bilaterally. His corneas exhibited bilateral fine grey haze with sclerotic scatter indicating stromal oedema spreading peripherally but there was no evidence of epithelial defect, infiltrate nor keratic precipitate. Pupils were equal and reactive with no evidence of relative afferent pupillary defect. Corneal sensation was intact. There was no anterior chamber activity and intraocular pressures were within normal range.

He was pseudophakic in both eyes with clear lens implants. Dilated fundus examination was unremarkable. He had no previous history of corneal pathology and had undergone uncomplicated bilateral phacoemulsification with lens implants 20 years earlier with early onset cataracts due to diabetes. He had no reported eye problems on his yearly checks with the community optometrist for diabetic retinopathy screening up to a year earlier.

## INVESTIGATIONS

Specular confocal microscopy demonstrated reduced endothelial cell density (988 CD/mm<sup>2</sup> right and 737 CD/mm<sup>2</sup> left) with polymegethism. Anterior segment Optical Coherence Tomography (OCT) demonstrates bilateral corneal oedema with thickened Descemet (figure 1).

## DIFFERENTIAL DIAGNOSIS

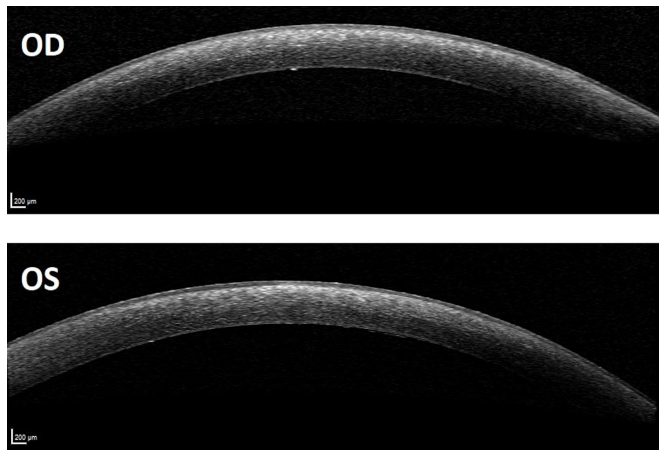
During his ICU admission, he was treated for COVID-19 pneumonia (SARS-CoV-2 RNA PCR positive from oropharyngeal swab and sputum). The eye-care protocol was completed daily and no acute ophthalmic signs were noted. Although he recovered from bronchopneumonia, he required intubated ventilation, inotropic support, flexible fibreoptic bronchoscopy for mucus plug, tracheostomy for respiratory wean and haemofiltration for acute kidney injury. His recorded oxygen saturation throughout ICU stay was maintained at 87% and above. CT head did not demonstrate any hypoxic brain injury. Available literature on hypoxic-related endothelial failure are only associated with localised ocular surface hypoxia in association with contact-lens wear rather than systemic hypoxia. Systemic hypoxia has instead been shown to influence collagen and matrix metalloproteinase, which has consequential effects on extracellular matrix (ECM) structure expression<sup>6</sup> in the stromal layer but not corneal endothelium. A prospective study also indicated that chronic hypoxia may induce ECM remodelling and losses in collagen framework content causing corneal stromal thinning, but has no effect on corneal endothelium.<sup>7</sup>

This patient did not receive any medications that could have caused corneal decompensation such as N-methyl-D-aspartate antagonist, amiodarone and menadione. The ocular surface was not exposed to toxic insults that could precipitate endothelial failure, such as benzalkonium chloride and chlorhexidine. We did not suspect endothelial failure due to surgery or endothelial dystrophy as he had no signs of corneal pathology for 20 years after cataract surgery.



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**Figure 1** Anterior segment Optical Coherence Tomography (OCT) demonstrating bilateral corneal oedema with thickened Descemet.

We therefore concluded that the cause of his acute bilateral corneal decompensation was SARS-CoV-2 viral endotheliitis, and corneal hypoxic injury secondary to acute systemic hypoxia.

### TREATMENT

As he did not have signs of active intra-ocular inflammation to warrant topical corticosteroid therapy, he was initially treated for his symptoms with G trehalose 3% and hyaluronic acid 0.15% and Oc carbomer 0.2% eye gel.

### OUTCOME AND FOLLOW-UP

At 1-month follow-up, best corrected visual acuities were 6/9 in the right eye and 6/9 in the left eye. His corneal oedema had resolved in the right eye and improved in the left eye, leaving behind diffuse subepithelial scarring (figure 2). This patient was commenced on G sodium chloride 5% four times a day to both eyes.

### DISCUSSION

This is the first reported case of COVID-19 (caused by the SARS-CoV-2 virus) causing bilateral diffuse endotheliitis leading to corneal decompensation, subepithelial scarring and long-term reduced vision. Recent updates provided by the American Academy of Ophthalmology discussed SARS-CoV-2 being detected in ocular secretions and ocular surface cells<sup>1</sup> as well as conjunctivitis and keratoconjunctivitis being presenting symptoms of COVID-19 in affected patients.<sup>3,4</sup> However, these ocular findings resolve with medical treatment and there are no reports on corneal decompensation and long-term effects on vision.

There is now strong evidence that SARS-CoV-2 uses human ACE2 as the receptor for entry.<sup>8–10</sup> Existing data on immunohistochemical analysis and surgical conjunctival specimens confirm expression of ACE2 and Transmembrane Protease Serine



**Figure 2** Anterior segment photos demonstrating subepithelial scarring.

Subfamily 2 (TMPRSS2) in the conjunctiva, limbus and cornea.<sup>11</sup> Mouse models deficient in ACE2 developed corneal oedema and chronic ocular surface inflammation,<sup>12</sup> which is very similar to our clinical findings. In vitro studies reveal that when ACE2 is downregulated or deficient, there is a corresponding increase in angiotensin II, leading to unregulated inflammation.<sup>13</sup> The corneal stroma contained a large numbers of CD11c, CD68 and CD3 positive cells. Interleukins (IL-1a, IL-1b), chemokines (CCL2, CXCL8) and Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) are all significantly elevated resulting in a cytokine storm-like phenotype.<sup>12</sup> Since COVID-19 binds to and reduces the expression of ACE2, the corneal inflammation in our post-COVID-19 patient may have similar mechanism with ACE2-deficient mice manifesting in corneal decompensation in the long term.

The association between ocular involvement and the severity of COVID-19 has also been analysed.<sup>14</sup> Guan *et al*,<sup>15</sup> who retrospectively analysed clinical characteristics of 1099 patients with COVID-19 and Wu *et al*,<sup>16</sup> who retrospectively investigated the ocular characteristics of 38 patients with COVID-19 both reported an increased incidence of ocular manifestation in patients with severe disease. Correlating to these findings, our patient with bilateral corneal decompensation developed a severe form of COVID-19 with acute respiratory failure requiring prolonged ventilation and inotropic support, and complications including acute kidney injury and pneumothorax.

While other viral pathogens such as cytomegalovirus, herpes simplex keratitis and myxovirus parotitis (mumps) virus are known to give rise to endotheliitis, the disease typically presents unilaterally and is accompanied by presence of uveitis.<sup>17</sup> This patient may have had some anterior chamber inflammation in the acute phase that was not noted due to delayed presentation. The patient only noticed symptoms of reduced vision on waking from 34 days of anaesthesia and ventilation. Regrettably clinical findings during the active stage of the disease are lacking. Retrospective eye swab testing for SARS-CoV-2 RNA PCR at symptoms onset would have been helpful during the acute phase.

### Patient's perspective

I had good vision in both eyes for most of my life. It was a shock to wake up from being on ICU for so long feeling weak in myself and also not to have my normal level of vision. I was told that I'd developed scarring in the eyes, that was hard to accept along side the tracheostomy that I woke up to find. Currently, I am using eye drops and I hope the vision will improve over time. I don't think anything could have been done to prevent this in my case. I wish my story would raise awareness of this disease and others could be diagnosed promptly in the future.

### Learning points

- ▶ Patients with severe COVID-19 bronchopneumonia may develop acute corneal decompensation due to viral endotheliitis.
- ▶ Prompt assessment allows for investigations within a narrow time frame.
- ▶ Early management may reduce severity of corneal scarring and long-term visual prognosis.
- ▶ There may be a role for routine ophthalmic examination in patients that have severe COVID-19 disease, and those receiving prolonged ventilation.

Anterior chamber paracentesis carried the risk of infection and lens damage, and is unlikely to yield further diagnostic and management value passed the acute stage.

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