



# Rejection of Acellular Porcine Corneal Stroma Transplantation During Coronavirus Disease 2019 Pandemic

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**Abstract:** To report 2 successfully managed cases of graft rejection with acellular porcine corneal stroma (APCS) transplantation in patients with fungal corneal ulcer. Two patients were diagnosed with fungal corneal ulcer and received APCS transplantation. Graft rejection developed due to the lost follow-up during the period of coronavirus disease 2019 outbreak. Amniotic membranes transplantation and cauterization of neovascularization was performed, respectively. The graft failure resolved successfully after the procedure. To the best of our knowledge, amniotic membranes transplantation and cauterization of new vessels are the firstly reported in treating APCS graft failure. Amniotic membranes transplantation or cauterization of neovascularization appear to be a safe and cost-effective method for treating graft failure.

**Key Words:** Acellular porcine corneal stroma, amniotic membranes, cauterization, COVID-19, rejection

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This study was approved by the Ethics Committee of Jilin University. Written informed consent was obtained from the patients.

Consent for publication: The patients presented in this case reports provided a written and signed informed consent.

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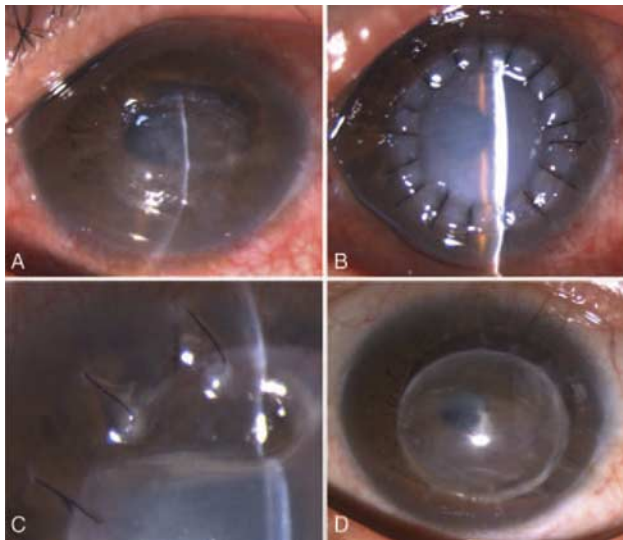
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Keratoplasty is the definitive treatment for most causes of corneal blindness and it is the most commonly performed procedure worldwide.<sup>1,2</sup> Shortage of donor corneas is regarded as a major limitation for keratoplasty.<sup>3</sup> Acellular porcine corneal stroma (APCS) transplantation has been developed to be an alternative option to substitute allografts due to its similarity to the human cornea in refractive status, thickness and size since 2012.<sup>4,5</sup> Acellular porcine corneal stroma is processed from fresh porcine corneas through removing cellular and nuclear materials.<sup>6</sup> Graft failure might occur in APCS transplantation similar to human cornea. We herein report 2 graft rejection cases with APCS due to the lost follow-up during the period of coronavirus disease 2019 (COVID-19) outbreak.

## CLINICAL REPORT

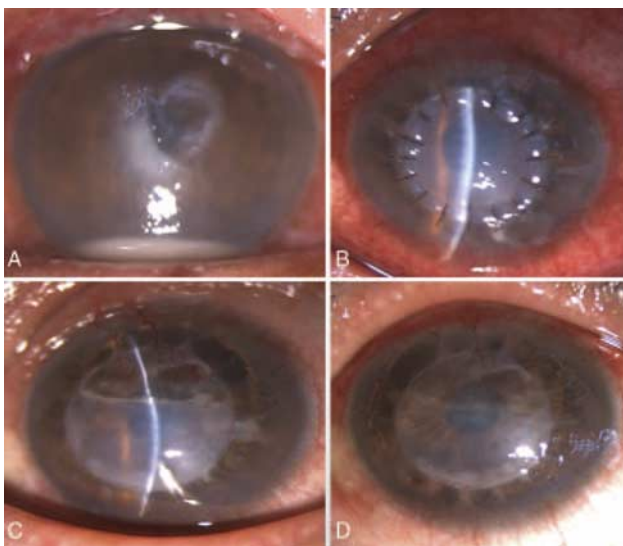
A 61-year-old male patient presented to the Department of Ophthalmology in October 2019 with a history of redness, decreased visual acuity and foreign body sensation in his left eye since last 2 weeks. On examination, his visual acuity was counting fingers at 40 cm and intraocular pressure was normal in left eye. Slit-lamp examination revealed conjunctival congestion and cornea ulcer of approximate 5 × 4 mm at the central and inferior cornea in left eye (Fig. 1A). In vivo confocal microscopy (IVCM) showed a large amount of bamboo-like high reflection. Diagnosis of fungal corneal ulcer was made based on clinical examination and IVCM results. Debridement was done under topical anesthesia. Topical levofloxacin (Santen Pharmaceutical Co., Ltd, Osaka, Japan), tobrex (s.a. Alcon-Couvreur n.v., Puurs, Belgium), natamycin (Alcon Laboratories, Inc, Texas, USA), voriconazole (Sichuan Medco Huakang Pharmaceutical Co., Ltd., Sichuan, China) were administered hourly along with itraconazole (Xian Janssen Pharmaceutical Ltd., Xian, China) 200 mg orally. There was no improvement after the treatment. Finally, lamellar keratoplasty was performed with APCS (AiNear Corneal Engineering Corporation, Shenzhen, China) under general anesthesia. On postoperative day 2, slit-lamp examination showed mild conjunctival congestion, cornea edema and intact sutures with graft in position (Fig. 1B). The follow-up was lost for months due to the COVID-19's epidemic outbreak. The patient presented again at 5 months after surgery. On slit-lamp examination, the graft was melted at the superior cornea from 10:00 AM to 12:00 AM position with approximate a size of 4 × 2 mm (Fig. 1C). The loose sutures were removed, followed by corneal scraping and double-layer amniotic membranes transplantation. Furthermore, the cornea was covered by a bandage contact lens. After the transplantation, topical



**FIGURE 1.** (A) Slit-lamp examination of the left eye showing conjunctival congestion and cornea ulcer of approximate 5 × 4 mm at the central and inferior cornea. (B) Slit-lamp examination of the left eye postoperatively, showing mild conjunctival congestion, cornea edema, the well positioned and intact sutures. (C) Slit-lamp examination revealed the melted graft at the superior cornea from 10:00 AM to 12:00 AM position with approximate a size of 4 × 2 mm. (D) The ocular surface was quiet at 7-month follow-up.

medications of levofloxacin (Santen Pharmaceutical Co., Ltd., Osaka, Japan) hourly and fluoromethalone (Santen Pharmaceutical Co., Ltd., Osaka, Japan) 3 times per day were prescribed. The sutures were removed on postoperative day 20. The corneal status was stable at the 7-month follow-up (Fig. 1D).

A 56-year-old male was referred to our department in October 2019 with a week history of redness, gradually worsening ocular pain and decreased vision in the left eye after injury with



**FIGURE 2.** (A) Slit-lamp examination revealed conjunctival congestion and ulcer of approximate 5 × 5 mm in the central cornea with hypopyon and feathery margin. (B) Slit-lamp examination postoperatively showed cornea edema, opacity with intact sutures, a shallow anterior chamber and aqueous flare. (C) Slit-lamp examination showed conjunctival congestion, melting graft at the superior 1/3 cornea and 2 robust vessels extending to the cornea from the superior direction. (D) New vessels were regressed obviously at 2-month follow-up.

sawdust. On initial examination, his visual acuity was counting fingers at 30 cm and intraocular pressure was normal in left eye. Slit-lamp examination revealed conjunctival congestion and ulcer of approximate 5 × 5 mm in the central cornea with feathery margin and Hypopyon (Fig. 2A). In vivo confocal microscopy showed a large amount of bamboo-like high reflection. The diagnosis of fungal corneal ulcer was made according to the patient’s clinical examination and IVCM findings. Topical levofloxacin (Santen Pharmaceutical Co., Ltd., Osaka, Japan) 6 times daily, tobrax (s.a. Alcon-Couvreur n.v., Puurs, Belgium) 6 times daily, natamycin (Alcon Laboratories, Inc, Texas, USA) hourly along with oral itraconazole (Xian Janssen Pharmaceutical Ltd., Xian, China) 200 mg daily were administered. Corneal scraping was done under topical anesthesia. There was no improvement in spite of medications were prescribed. The patient received lamellar keratoplasty with APCS (AiNear Corneal Engineering Corporation, Shenzhen, China) under general anesthesia. Slit-lamp examination at 6 days postoperatively showed cornea edema and opacity with intact sutures, a shallow anterior chamber and aqueous flare (Fig. 2B). The follow-up was lost due to COVID-19’s epidemic. The patient showed up again at 6months after surgery. Slit-lamp examination showed conjunctival congestion, graft melting at the superior 1/3 cornea and 2 robust vessels extending to the cornea from the superior direction in the left eye (Fig. 2C). Cauterization of neovascularization was performed. Topical autologous serum hourly and tacrolimus (Senju Pharmaceutical Co., Ltd. Osaka, Japan) 4 times daily were prescribed. New vessels regressed obviously on postoperative day 4. The corneal status was stable at 2-month follow-up (Fig. 2D).

**DISCUSSION**

In recent years, bioengineering corneas and corneal xenotransplantation have been developed rapidly to meet the shortages of donor tissues in treating corneal blindness.<sup>4</sup> Acellular porcine corneal stroma has been applied clinically since 2012.<sup>7</sup> Acellular porcine corneal stroma has been testified in a very limited number of clinical practices.<sup>8</sup> Acellular porcine corneal stroma transplantation may not be suitable in treating peripheral corneal diseases.<sup>9</sup> Graft failure may occur in APCS transplantation similar to human corneas (Supplementary Digital Content, Table 1, <http://links.lww.com/SCS/D516>).<sup>19</sup> Risk factors for human graft failure have been reported, including corneal neovascularization, repeat transplantation, grafts in larger size, inflammation, loose sutures, increased intraocular pressure, dry eye disease, and many other unknown factors.<sup>8,10–12,22</sup> Tacrolimus, glucocorticoid, or antiviral drugs and regrafting have been reported in treating APCS graft failure.<sup>4,5</sup>

Postoperative follow-up is critical for positive prognosis. This report illustrated 2 cases of APCS graft failure under the COVID-19 epidemic. One case was successfully managed with amniotic membranes transplantation, and the other with cauterization of new vessels. To the best of our knowledge, amniotic membranes transplantation and cauterization of new vessels are the firstly reported in treating APCS graft failure.

For patient 1, APCS graft melting and loosening sutures were encountered because of the lost follow-up during the period of COVID-19 outbreak. Loose sutures promote the growth of blood and lymphatic vessels, which lead activated immune cells to enter the graft bed and drives initiation and development of rejection through the process of inflammation, scarring or edema of the graft.<sup>2,11</sup> Amniotic membranes transplantation

and bandage contact lens application were performed in the rehabilitation of ocular surface.<sup>18</sup> First, the basement membrane of the amniotic membranes is similar to that of the cornea and conjunctiva in structure and composition. It provides a substrate for epithelial cells grow, migrate, regenerate easily, and promotes formation of new tissues.<sup>13</sup> Second, amniotic membranes reduces inflammation and serves as a physical barrier to prevent the infection entering the inner eyes because of its close attachment to the ocular surface.<sup>14</sup> Third, its potent antiangiogenic effects contribute to inhibition of blood vessels and graft failure.<sup>15</sup> For patient 2, neovascularization was present in the superior quadrant of the cornea.<sup>20</sup> The growth of corneal neovascularization resulted in exudates, fibrosis, inflammation and hemorrhage, threatening the survival of the graft.<sup>11,16</sup> The pathological corneal vessels act as a high-efficiency corridor to allow host immune effector elements travel to the graft bed and accelerate graft rejection.<sup>16</sup> Cautery of new corneal vessels produces a safe and effective way to stop migration of immune effector cells to the graft site and reduce the risk of graft rejection.<sup>17,21</sup> In patient 2, neovascularization gradually regressed and the graft healed well after cauterization.

### CONCLUSIONS

The study is the first to illustrate the successful managements of the APCS graft failure under the COVID-19 epidemic with amniotic membranes transplantation or cauterization of neovascularization, which will be valuable for the future clinical practices of APCS, including patient selection and postoperative management. Postoperative follow-up is critical for positive prognosis in APCS transplantation.

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