Clostridium perfringens Endophthalmitis After Penetrating Keratoplasty With Contaminated Corneal Allografts: A Case Series

Joshua H. Hou, MD, Anjali Tannan, MD,† Jonathan B. Rubenstein, MD,† Osvaldo I. Lopez, MD,‡ Kristen McCoy, CEBT,§ Randy J. Epstein, MD,† Richard J. Grostern, MD,† and Joel Sugar, MD**

Purpose: To report the postoperative clinical course of 3 patients who underwent corneal transplantation with corneal allografts contaminated with *Clostridium perfringens* and to evaluate the risk factors for anaerobic contamination in 2 donors.

Methods: Patient records and adverse reaction reports from a single eye bank related to cases of posttransplant *C. perfringens* endophthalmitis were reviewed. Records regarding the mated corneas, donor autopsy reports, and other pertinent data were also reviewed.

Results: Three adverse reactions associated with transplantation of corneal allografts contaminated with *C. perfringens* were reported. Two cases were from mated corneas. Both patients developed fulminant endophthalmitis after undergoing uncomplicated penetrating keratoplasty and required subsequent enucleation. Another isolated case (with no adverse reaction in the mate cornea) developed hypopyon postoperatively that resolved with intravitreal and topical antibiotics. Possible risk factors for anaerobic tissue contamination in the donors included illicit drug use in the first donor and exposure to sewage at the time of death in the second donor.

Conclusions: Clostridial endophthalmitis is an aggressive rapidly progressive infection with potentially poor visual outcomes that can be transmitted from infected corneal allografts. Further investigation is needed to clarify the role of anaerobic donor rim cultures and the donor risk factors associated with recovering corneal allograft tissue contaminated with *C. perfringens*.

Key Words: endophthalmitis, penetrating keratoplasty, *Clostridium perfringens*

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From the *Department of Ophthalmology and Visual Sciences, University of Illinois Eye and Ear Infirmary, Chicago, IL; †Department of Ophthalmology, Rush University Medical Center, Chicago, IL; ‡Chicago Eye Institute, Chicago, IL; and §Midwest Eye-Banks, Ann Arbor, MI.

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Reprints: Joel Sugar, MD, 1855 W. Taylor St, Suite 3.164, Chicago, IL 60612 (e-mail: joelsuga@uic.edu).

Clostridium perfringens is a spore-forming anaerobic bacillus that is ubiquitous in the environment.[1] Intraocular inoculation of *C. perfringens* by trauma, surgery, or endogenous spread can result in fulminant endophthalmitis with very poor outcomes.[2–9] Most cases published to date have ended in enucleation.[2,3] Specific reports of postkeratoplasty clostridial endophthalmitis due to contaminated corneal allografts are extremely rare. To the best of our knowledge, there have only been 2 reported cases, both of which resulted from transplantation of a single pair of contaminated mated corneas.[9] Because of rarity of postkeratoplasty clostridial endophthalmitis, little is known regarding prognosis or treatment options. Furthermore, donor risks factors that may contribute to clostridial contamination in donor corneal tissue remain poorly defined.

We observed 4 cases, two with fulminant endophthalmitis, one case of intraocular inflammation due to possible infection, and one case with no adverse outcomes after transplantation of corneal allografts contaminated with *C. perfringens*. The clinical course, outcomes, donor characteristics, and donor risk factors are discussed.

CASE SERIES

Patient 1

A 67-year-old man, with a history of diabetes mellitus, hypertension, end-stage renal failure on dialysis, and prior trauma after surgical repair in the right eye 30 years previously, presented with aphakic bullous keratopathy in the right eye. He underwent uncomplicated penetrating keratoplasty (PKP) using tissue from donor 1, anterior vitrectomy, and sutured intraocular lens (IOL) placement in the right eye. The donor rim and medium were sent by the surgeon for routine aerobic and anaerobic cultures. The patient was seen in the morning on postoperative day (POD) 1 and was noted to have hand motions vision with moderate corneal edema but no infiltrates in the graft, intact sutures, well-positioned IOL, and minimal anterior chamber reaction. The patient was instructed to follow up postoperative week 1 per routine.

The surgeon was then notified that afternoon, 22 hours after the initial cultures were sent, of preliminary growth of gram-positive rods from the donor rim and storage medium cultures. Approximately 21 hours later, on POD 2, the patient

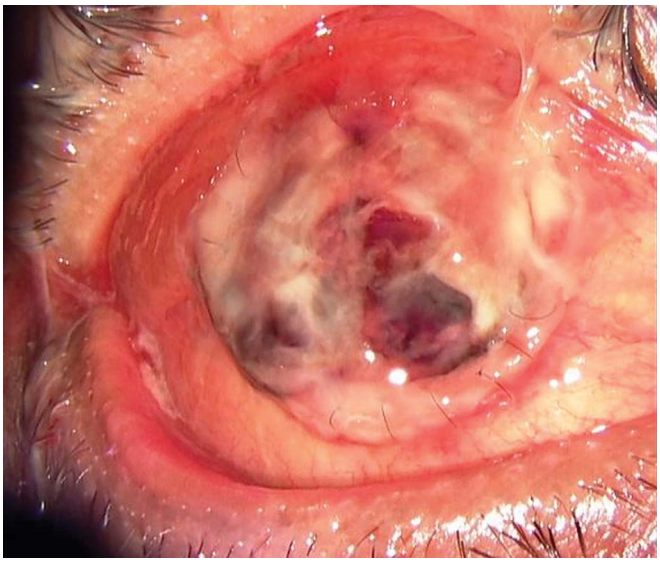

FIGURE 1. Intraoperative photograph of patient 1 on POD 3 demonstrates purulent necrosis of host corneal tissue with complete absence of the corneal graft in the right eye. There is exposure of the IOL inferonasally. Hemorrhage and purulent material is noted behind the IOL.

returned urgently, complaining of "blood coming out of the eye." Visual acuity was no light perception (NLP) in the right eye. He had intense lid chemosis and conjunctival injection. There was diffuse infiltration and necrosis of the host cornea with multiple loose sutures and areas of the uvea prolapsed at the graft–host junction. The central corneal graft appeared clear with stable edema. His anterior chamber demonstrated 100% hyphema with no view of the IOL. He was admitted to the hospital and administered intravenous (IV) vancomycin and piperacillin/tazobactam and fortified topical tobramycin (15 mg/mL) and vancomycin (50 mg/mL) every hour. On POD 3, complete melt of the corneal graft was noted (Fig. 1). The patient underwent enucleation of the right eye on POD 3. The final anaerobic culture results from the donor rim and storage medium, the corneal cultures taken on POD 2, and the intraoperative cultures taken on POD 3 all showed *C. perfringens*. Widespread necrosis of anterior segment and posterior segment intraocular structures was noted on pathology (Fig. 2). Gram stain confirmed the presence of numerous gram-positive rods within the globe and in areas of necrosis (Fig. 2B).

The patient completed 1 week of systemic antibiotics. Preliminary blood cultures were negative, and he later underwent orbital reconstruction with a dermis fat graft with no evidence of extraocular spread of infection.

Patient 2

An 88-year-old monocular woman, with a history of diabetes mellitus, coronary artery disease, and end-stage chronic open-angle glaucoma, presented with pseudophakic bullous keratopathy in her only functional eye (left eye). She underwent uneventful PKP using tissue from donor 1. The donor rim and media were sent for routine cultures by the surgeon.

On POD 1, her visual acuity was counting fingers at 6 inches. The graft was clear with a deep anterior chamber, and she was instructed to follow up postoperative week 1 per routine. The surgeon was then notified that evening, 29 hours after the initial cultures were sent, of gram-positive rods on preliminary cultures of the donor rim and medium. Approximately 14 hours after that on POD 2, the patient returned urgently with severe mucopurulent discharge and pain in the left eye. Visual acuity was NLP. Significant eyelid edema and conjunctival injection were noted. She had moderate corneal edema with iris details visible. The patient was taken to the operating room as an emergency that day. The discharge was cultured and a "tap and inject" was performed using intravitreal vancomycin and ceftazidime. The patient was admitted to the hospital and administered IV vancomycin, IV piperacillin/tazobactam, oral ciprofloxacin, topical fortified vancomycin (50 mg/mL), and topical fortified tobramycin (18 mg/mL) every hour. The final donor rim cultures were positive for *C. perfringens* and *Pediococcus pentosaceus* and final donor medium cultures were positive for *C. perfringens*. The patient developed cellulitis of the lids and face and was offered enucleation, but she refused. She remained in the hospital on IV antibiotics for 2 weeks. Cultures from the discharge and vitreous tap showed no growth of aerobes, anaerobes, or fungus. However, on POD 13, there was

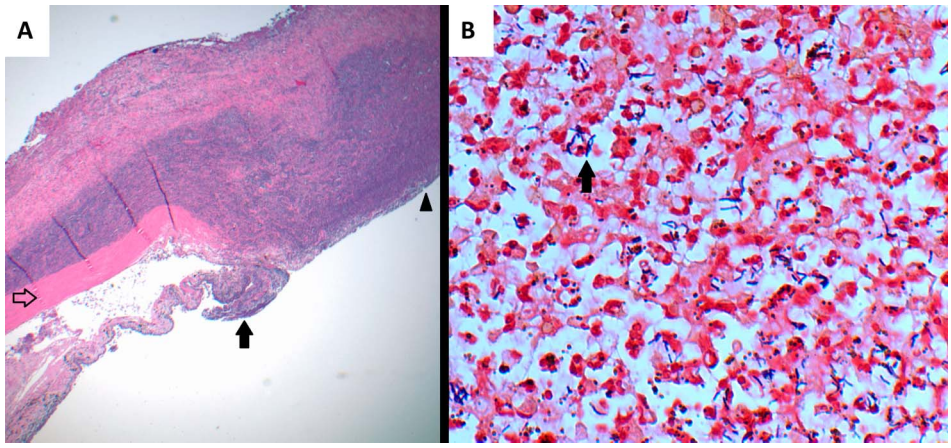

FIGURE 2. A, Hematoxylin and eosin stain showing the limbus from the enucleated globe of patient 1. There is diffuse inflammatory infiltrate and necrosis of the cornea (arrowhead) and iris (black arrow) with an intact outer sclera (clear arrow). B, Gram stain showing many gram-positive rods (arrow) in the vitreous cavity consistent with positive intraoperative cultures for *Clostridium perfringens*.

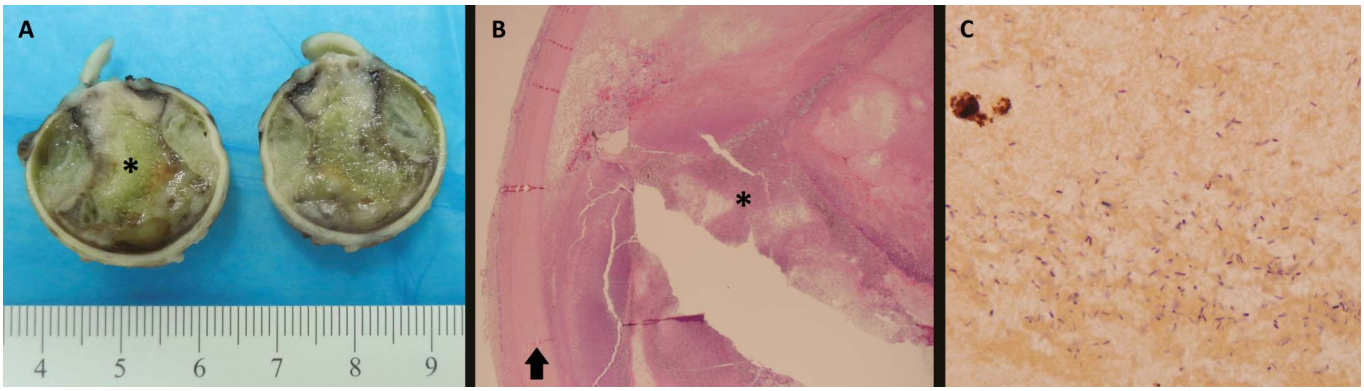

FIGURE 3. A, Gross pathology specimen from patient 2 with purulent material (*) filling the globe. B, Hematoxylin and eosin staining of relatively intact scleral (arrow) and diffuse inflammatory necrotic debris in the vitreous cavity (*) (original magnification ×20). C, Gram stain showing numerous gram-positive rods consistent with *Clostridium perfringens* (original magnification ×1000).

worsening of facial cellulitis despite the antibiotic regimen. At that point, the patient consented to enucleation of the left eye. Pathology (Fig. 3) was consistent with endophthalmitis without evidence of extraocular extension. Gram stain was notable for numerous gram-positive rods throughout the globe (Fig. 3C).

Donor 1

Donor 1 was a 63-year-old man with a history of hypertension, borderline diabetes mellitus, gout, chronic pain, and prescription pain medication use. Cause of death was cardiopulmonary arrest with multiple blunt force injuries after a motor vehicle accident. Death to body refrigeration time was 4.5 hours. Death to recovery time was 19 hours 49 minutes for the right eye and 19 hours 54 minutes for the left eye. Death to transplantation time was 5 days in both cases. Only ocular and bone/tendon tissue were recovered from this donor.

His surgical history was positive for bilateral hip replacement approximately 1 year previously and social history was positive for a history of cocaine abuse 28 years previously, history of smoking, and recent history of prescription pain medication abuse. There was no documented history of IV drug use; however, police reports from the scene of the accident did find a "clear plastic bag containing a green leafy substance and a small bottle with an attached spoon containing an unknown white powdery substance." Preprocedural testing was negative for hepatitis B surface antigen and antibody, HBV PCR, hepatitis C antibodies, HCV PCR, HIV-1 and HIV-2 antibodies, HIV-1 PCR, HTLV 1-2 PCR, and West Nile virus PCR. Multiple cultures obtained from the donor's bone and tendon tissue samples, including both femurs and associated hardware, both humeri and rotator cuffs, both tibias, left anterior and posterior tibialis tendons, and the left peroneus longus muscle, were found to be positive for *C. perfringens* 8 days after both corneas had been transplanted.

Final blood toxicology report was positive for caffeine, clonazepam, morphine, amphetamines, and diphenhydramine. Urine toxicology was positive for cannabinoids, amphetamines, opiates, and benzodiazepines, but negative for heroin. The final autopsy report noted multiple injuries from blunt force trauma, morphine, and amphetamine intoxication, but no clear evidence of IV drug abuse.

Patient 3

Patient 3 was a 59-year-old man with a history of granular corneal dystrophy who underwent uncomplicated PKP in the right eye using tissue from donor 2. The donor rim and media were sent for routine cultures. On POD 1, his visual acuity was 20/250 with moderate injection, with moderate corneal striae. Approximately 27 hours after the donor rim and medium were sent for cultures, the surgeon was notified by the laboratory of preliminary results showing gram-positive rods only in the corneal storage medium.

The patient then returned on POD 5 with complaints of increased pain and blurry vision. He was found to be noncompliant with his postoperative drop regimen. Visual acuity had declined to counting fingers at 1 foot. He had moderately severe corneal striae and 1-mm hypopyon in the anterior chamber. An anterior chamber tap was taken. Intravitreal injections of vancomycin and ceftazidime as well as subconjunctival injections of vancomycin and tobramycin were given. Topical moxifloxacin 0.5% every hour and prednisolone acetate 1% every 2 hours were also started.

The patient had rapid improvement of his vision and anterior chamber inflammation. By POD 6, visual acuity was 20/300 with trace residual hypopyon. On POD 7, the surgeon was notified of final culture results showing rare gram-positive bacilli resembling *Carnobacterium maltaromaticum*, rare *Escherichia coli*, rare *Streptococcus gordonii,* and rare *Enterococcus faecalis* in the donor medium; and also rare *lactobacillus*, rare *E. coli*, and rare *C. perfringens* in the donor rim. The recipient aqueous and vitreous cultures were negative for organisms.

The patient continued to do well and his topical antibiotic regimen was tapered on POD 11. His visual acuity 2 months later was 20/80, pinhole 20/50, in the right eye with a clear corneal graft and no evidence of anterior chamber inflammation.

Patient 4

Patient 4 was a 53-year-old man with no medical history who presented with decreased vision secondary to

keratoconus in the left eye. He underwent uncomplicated PKP in the left eye using tissue from donor 2. The donor rim was sent for routine culture. The patient had an uncomplicated postoperative course and his best-corrected visual acuity 3 months later was noted to be 20/60 with a clear graft and no evidence of infection or inflammation. The donor rim cultures grew *E. coli* and Enterococcus; however, anaerobic cultures were not performed.

Donor 2

Donor 2 was a 48-year-old man with a history of sleep apnea, patellofemoral syndrome, and chest pain, who died from hemorrhagic shock after an industrial explosion. He was using a blowtorch on a large sewage tanker. It is believed that methane gas caught fire from the torch and caused a large explosion. Prerecovery testing was all negative including hepatitis B surface antigen and antibody, hepatitis C antibody, HIV-1 and 2 antibodies, RPR, and HIV-1/HBV/HCV PCR. Death to body refrigeration time was 7 hours and 46 minutes. Death to recovery time was 10 hours 53 minutes for the right eye and 11 hours 1 minute for the left eye. Death to tissue transplantation time was 6 days for the left eye (tissue transplanted to patient 4) and 8 days for the right eye (tissue transplanted to patient 3). Toxicology was negative for any drug or alcohol use. Autopsy report was notable for hemorrhagic shock from a perforated lower abdominal wound without evidence of bowel perforation.

DISCUSSION

Before this series, only 2 other cases of postkeratoplasty *C. perfringens* endophthalmitis have been reported.[9] In both cases, endophthalmitis developed within 12 to 24 hours of surgery. The infected eyes were salvaged following vitrectomy and aggressive antibiotics, but with poor visual outcomes.[9] In 2 cases presented here, rapid progression of infection despite aggressive antibiotic therapy ultimately led to enucleation. The fulminant course of endophthalmitis in this case series and in previously reported cases highlights the overall poor prognosis and the need to explore better treatment and prevention options.

Several classic signs of *C. perfringens* endophthalmitis associated with trauma, surgery, or endogenous spread have been reported. These include rapid onset with severe pain, rapid loss of vision, swelling of the eyelid, elevation in ocular tension, coffee-colored discharge in the anterior chamber, and gas bubbles in the anterior chamber.[3] Although the first 3 signs were present in 2 of our cases, coffee-colored discharge and gas bubbles were not noted. Given the primary involvement of the cornea with rapid melting, it is possible that those signs could have been missed. Alternatively, those signs may have been absent due to the fact that in both our cases of postkeratoplasty endophthalmitis, the contaminated graft, rather than the posterior chamber or vitreous cavity, was the primary nidus of infection.

Anaerobic cultures of donor corneoscleral rims are often not ordered by surgeons given the low prevalence of anaerobic infections, added cost, and questionable clinical utility.[10] Given the small number of cases of postkeratoplasty clostridial endophthalmitis, there is insufficient evidence to support anaerobic donor rim cultures at this time. However, several points regarding anaerobic donor rim cultures are worth noting here.

First, if cultures are obtained, turnaround times for donor rims contaminated with *C. perfringens* can be quite fast and may provide early indication of a pending infection. Although culture turnaround times may vary depending on the bacterial load of the specimen and the protocols used by different laboratories, *C. perfringens* is known to be one of the fastest growing bacterial species with generation times below 8 minutes under ideal conditions.[1,11]

In the 2 cases reported here, where the bacterial load in the contaminated allograft was sufficient to cause fulminant endophthalmitis, the turnaround time for rim cultures was 22 hours and 29 hours, respectively. In contrast, in the third case, where donor rim cultures took 7 days to grow only rare *C. perfringens* and no *C. perfringens* was ultimately found in the corneal storage medium, the patient developed a far less fulminant reaction that responded well to antibiotic treatment and may not have been a true *C. perfringens* infection.

Clinical utility of anaerobic cultures remains questionable; however, rapid growth of *C. perfringens* on donor rim cultures may be suggestive of a higher bacterial load in the contaminated allograft and may be more worrisome. Rapid turnaround from cultures may also offer a window of opportunity for intervention. In both cases reported here, patients were asymptomatic on POD 1 but then became NLP by POD 2. Also, in both cases, culture results were available in the interim. It is impossible to know whether initiating aggressive therapy when preliminary culture results first became available would have been helpful to our patients because we do not know exactly when they became NLP. However, further research with careful clinical observation of future cases is warranted.

There is evidence that early vitrectomy can improve outcomes in cases of penetrating trauma-related clostridial endophthalmitis.[6–9] However, in most cases where this has been reported, patients were already symptomatic at the time of vitrectomy surgery. There is no evidence to support prophylactic vitrectomy for clostridial endophthalmitis based only on preliminary culture results, although good outcomes were achieved in 1 case in the literature where a "prophylactic" vitrectomy was performed as part of an open-globe repair after penetrating injury.[7] The patient achieved 20/25 vision despite the fact that vitreous aspirate grew *C. perfringens* after the surgery.[7] Of note, although corneal explantation to remove the original nidus of infection may seem to be another reasonable option in cases of postkeratoplasty *C. perfringens* endophthalmitis, in the 2 cases reported by the Centers for Disease Control and Prevention, the globe was salvaged with vitrectomy and antibiotics alone.[9] Because of rapid progression of the disease process and early involvement of the anterior segment, vitrectomy was not possible by the time our patients presented with symptoms. Further research is needed to determine the appropriate next step in cases where an early donor rim culture result is available and shows anaerobic gram-positive rods.

One important step to consider in the future may be immediate temporary quarantining of the mate cornea (if possible) in cases where a surgeon obtains a rapidly positive culture for anaerobic gram-positive rods. In both cases of fulminant endophthalmitis presented here and in both cases published previously by the Centers for Disease Control and Prevention, mated corneas were involved and had similar outcomes.[9] Although the small number of cases precludes any formal recommendation, further observational research regarding concordance of outcomes between mate corneas if one is contaminated with *C. perfringens* is warranted.

The risk factors for anaerobic contamination of corneal donor buttons remain unclear. Risk factors for bacterial contamination in general, most commonly *Staphylococcus epidermidis*, include donor death from septicemia, malignancy, history of prolonged ventilator use, and cardiac death.[12,13] Donor gender, age, time from death to corneal tissue recovery, and time from tissue recovery to transplantation have not been found to be risk factors for contamination.[12] Abdominal cancer is the most concerning known risk factor for *C. perfringens* bacteremia.[14] In this case series of *Clostridium* endophthalmitis, no clear risk factors precluded tissue donation in either donor based on standard screening protocols. However, other risk factors related to the 2 donors may have been worth considering. In the first donor, history of illicit drug abuse (even without evidence of IV drug abuse) may have warranted careful examination of the body for needle tracks along the arm, legs, or groin, or under the tongue to rule out IV drug abuse. The presence of bilateral hip prostheses that were infected on autopsy may have been a potential source for chronic bacteremia in a possible IV drug abuser. For the second donor, exposure to sewage with a concurrent penetrating abdominal injury at the time of death was also a concern for anaerobic contamination. Further investigation on risk factors for donor tissue contamination with *C. perfringens* is warranted.

In conclusion, *C. perfringens* can cause a devastating postkeratoplasty endophthalmitis after transplantation of corneal allograft tissue contaminated with *C. perfringens*. Further research will be necessary to determine the utility of anaerobic donor rim cultures and identify donor risk factors associated with clostridial contamination of corneal allograft tissue.

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